The Manitoba Medical Review

Vol. 39 MAY, 1959 No. 5

Medicine

Some Clinical Aspects of Adrenocortical Hyperactivity

E. Perry McCullagh, M.D.

Adrenocortical hyperactivity almost always is associated with cortical hyperplasia, adenoma, or carcinoma. When it is caused by hyperplasia, it is rarely associated with pituitary hyperactivity or tumor. In some patients having adrenocortical hyperactivity the size and weight of the adrenal gland are normal but the cellular appearance is consistent with that of hyperactivity. In some patients with hyperplasia or tumor multiple adrenal functions are hyperactive, whereas in others it appears that a single hormone is produced in excess.

Cases of adrenocortical hyperactivity can be divided into three groups on the basis of the type of hormone having the predominant effect. In the first group are conditions caused by excessive androgens; in the second, those caused by excessive hydrocortisone and similar substances; and in the third, those resulting from excessive electrolyte-controlling hormones, such as aldosterone. Usually the relatively pure effects of one type of hormone are seen, but the effects sometimes are those of two or more types of hormones.

The clinical symptoms of conditions in the first group are those of various types of adrenogenital syndrome; of conditions in the second, those of Cushing's syndrome; and conditions in the third, those of primary aldosteronism.

Histology

It is doubtful whether the normal adrenal cortex from a human being ever has been completely and accurately described. Specimens obtained at necropsy have undergone changes within an hour after death, and even operative specimens may be altered by the stresses of anesthesia and surgery.

Three separate zones of the adrenal cortex function as two separate glands. The outer layer, or zona glomerulosa, is under little influence by corticotropin (ACTH). This zone is thought to be the source of aldosterone. In normal persons venous blood and urine contain aldosterone, and its production is regulated physiologically largely by serum sodium concentration. Increased secretion of aldosterone is caused by depletion of sodium, increase in potassium, and lowered volume of extracellular fluid, particularly the volume of fluid within the vascular system. It has been shown in animals that occlusion of the inferior vena cava near its superior portion has a powerful influence upon increasing the production of aldosterone[1, 2] and that stretching of the right atrium causes a fall in its production.[3] These peripheral stimuli require intact carotid sinus nerves to complete the reflex.[2] A similar effect can be brought about by increasing the volume of intravascular fluid by addition of albumen to the blood. This decreases the output of aldosterone and has been shown to be independent of the sodium concentration in the circulation. A very brief and transient increase in aldosterone output can be brought about by ACTH. The most recent information available on the control of production of aldosterone was made public for the first time at the Laurentian Hormone Conference in Michigan in September 1958. Farrell has shown that after injection of extracts of beef hypothalamus into dogs a marked and sustained increase in production of aldosterone occurs as measured in the adrenal venous blood. These effects are present even when the animal is decerebrated and hypophysectomized. Farrell has also shown that an extract made from the posterior hypothalamus and including the pineal gland causes the greatest increase in production of aldosterone. This newly discovered hormone from the hypothalamus or the pineal or both he has named glomerulotropin.[4]

In the middle zone of the cortex, the zona fasciculata, the cells are large, clear, and arranged loosely in radial bands or cords. The inner zone, or zona reticularis, is composed of denser, more compactly arranged cells. These two zones are directly affected by ACTH and have reciprocal functions. The zona fasciculata, when under little stress, has a high content of cholesterol and lipids, but has a low content of enzymes. The zona reticularis, on the other hand, is relatively free of lipids but has a high content of enzymes; both acid and alkaline phosphatases, dehydrogenase, and ribonucleic acid. Under the impact of ACTH, cells of the zona reticularis spread toward the zona fasciculata, which shrinks. After administration of 100 mg. of ACTH daily for four days, cells that look like those of zona reticularis have taken up almost all of the space previously occupied by those of the zona fasciculata.[5]

Thus the zona fasciculata may be considered to be a storehouse of precursors of both androgens and corticoids, while the zona reticularis is the site of biosynthesis, the factory in which the end products are produced. It appears that both types of

From the Department of Endocrinology, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Presented at the 50th Anniversary of the Manitoba Medical Association, October 8, 1958.

steroids are produced by the same cells. The cellular origin of adrenal estrogens is not known.

Assays of Hormones in Diagnosis

There are several types of adrenal androgens. Three have been obtained in crystalline form from adrenocortical extracts. They are androstenedione; adrenosterone; and androstane 3 beta, 11 beta-diol-17-one.[6] Human adrenal venous blood has yielded delta^4-androstene-3, 17-dione and 11-beta-hydroxy-delta^4-androstene-3, 17-dione.[7] In intrauterine life an excess of adrenal androgens always is associated with adrenal hyperplasia; in early childhood it is more frequently associated with tumor than hyperplasia. Later in life, hyperfunctioning adenoma or carcinoma is present in about 20 per cent of patients with this disorder.

Tests employing assays for hormones have special value in the diagnosis of adrenal disease. In children, a normal value for urinary 17-ketosteroids or 17-hydroxycorticoids is 1.0 mg. per day or less. In women, normal amounts of urinary 17-ketosteroids range from 4 to 16 mg. daily and the 3-beta fraction is usually less than 20 per cent of the total. Urinary 17-hydroxycorticoids in women range from 2 to 9 mg. daily. If the urinary 17-ketosteroid values are more than 50 mg. daily adrenocortical adenoma or carcinoma usually is present. In some cases of carcinoma the amounts excreted exceed 1000 mg. per day, and in one of our patients the daily output was more than 1900 mg. per day.[8] In some cases of tumor, however, the amounts are normal. In about 70 per cent of patients having tumor the beta fraction exceeds 50 per cent of the total. In cases of adrenal dysfunction, such as pseudohermaphroditism, assays may show an excessive amount of urinary 17-ketosteroids and almost no 17-hydroxycorticoids. The presence of dehydroepiandrosterone or epiandrosterone seems to be an accurate indicator of the presence of cancer. In cases of adrenal carcinoma the types of excreted steroids may change greatly as the disease progresses.[9] Measurement of corticoids in the blood can be made, but it is not certain that it is more helpful from a diagnostic standpoint than their measurement in the urine. Newer tests may employ radioactive isotopes to measure rates of production of such steroids. The diagnosis of adrenal tumor based upon assays of hormones often may be sustained by intravenous pyelography, laminography, or presacral air studies, although surgical exploration often is necessary.

Suppression of the adrenal function with steroids or its stimulation with ACTH makes a useful adjunct to diagnostic tests. For suppression, a cortical steroid, preferably one that is highly active in doses of less than 5.0 mg. per day is given. The advantage of using strong preparations is that only a small amount of products from the administered material is excreted, thereby making it possible for the assay to reflect almost entirely the amounts of endogenous hormones. Doses of 9-alpha fluorohydrocortisone (1 to 2 mg. per day) or of prednisone (10 to 20 mg. per day) for a few days will rapidly suppress the normal adrenal function to the extent that urinary steroids almost completely disappear. In patients having adrenal hyperplasia, an extreme decrease in urinary steroids may occur; and in patients having tumor, little or no decrease usually occurs. There is, however, considerable overlapping of this effect.

Adrenal stimulation with 40 units of ACTH given intravenously may also be a helpful test. In the normal person, the ACTH test causes the urinary 17-ketosteroids and hydroxycorticosteroids to increase to as much as three times pretest values. The level reached after such treatment may remain within normal range but sometimes rises above normal values. In a person having tumor, little change usually occurs, and in a person having hyperplasia the response is greater than normal. In a patient having Cushing's syndrome the response to the ACTH test may be a five-fold increase in urinary steroids. In adrenogenital syndrome it is not uncommon to see high urinary levels of 17-ketosteroids associated with normal or low concentrations of corticoids. This discrepancy may be exaggerated by the ACTH test, but in some the urinary 17-ketosteroids may increase from 35 to 40 mg. daily while the corticoids increase from 2.5 to 15 mg. Unfortunately there is wide variation, and the test cannot be relied upon to differentiate hyperplasia from adenoma or carcinoma.

Clinical Syndromes Produced By Adrenocortical Hyperactivity

Adrenogenital Syndrome

In this condition the presence of an excess of masculinizing hormones produces a striking variety of clinical changes, depending upon age and sex. If the abnormality is present in the first few weeks of intrauterine life, the clinical picture is of one type. If it begins during late prenatal development or in early childhood, the effects are different, and if it arises after puberty, the clinical evidences differ further. In girls the effects differ more with the age of onset than they do in boys.

Pseudohermaphroditism

In girls affected by excesses of adrenal androgens in early intrauterine life, abnormal development of the genitalia occurs, causing a type of female pseudohermaphroditism. The baby is born with a large phallus often mistaken for a penis. There may be hypospadias; or a relatively large vagina-like urogenital sinus may remain, into which the urethra empties (Fig. 1). Ovaries and a hypoplastic uterus are present.

In some cases the excess of adrogen may be associated with a severe deficiency of hydrocortisone-like materials and perhaps other sodium-retaining substances resulting in marked loss of sodium. This appears to be due to an enzymatic

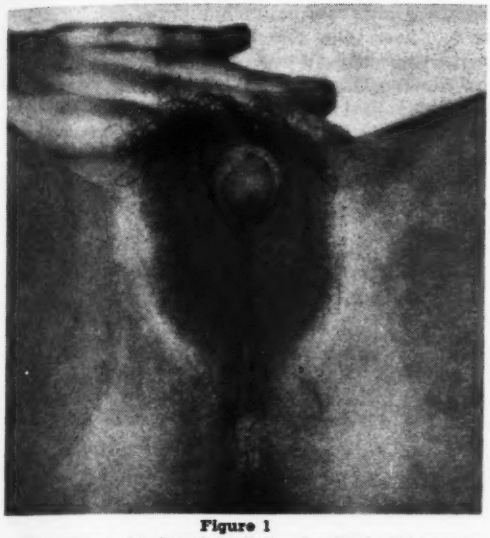


Figure 1

Appearance of external genitalia of patient with pseudohermaphroditism of adrenal origin.

disorder blocking normal pathways of steroid synthesis. In the past, weakness and vomiting in infants caused by a condition closely resembling Addisonian crisis often was undiagnosed or was mistakenly thought to result from pyloric stenosis. Recognition of the true condition and adequate treatment with cortisone-like substances alone or in conjunction with desoxycorticosterone or fluorohydrocortisone, may be life saving. The clinical clue may be in the deformity of the external genitalia as seen in pseudohermaphroditism in an infant girl or the presence of excessively large genitalia in an infant boy. The condition may appear in several members of the same family.

In a girl when this type of pseudohermaphroditism is unassociated with severe sodium loss and continues unrecognized until adulthood, the child may be reared as a boy and remain amenorrheic, without normal breast development and with other male characteristics. Adequate treatment with prednisone (Meticorten) or hydrocortisone suppresses the abnormal adrenals and will be followed by development of the breasts, a female figure, and normal menses. Wilkins[10] believes that such a disorder may be imposed on the infants of mothers treated during pregnancy with large doses of progesterone-like materials which are testosterone derivatives and have a coincident androgenic effect. In two such infants, the mothers had received intramuscular injections of progesterones.[8] 17-ethinyl testosterone is marketed under various names such as Progestoral, Lutocylol and anhydrohydroxyprogesterone.

In girls adrenogenital syndrome beginning late in intrauterine life or in prepuberal childhood mimics pubertas precox (macrogenito-somia precox) with varying degrees of masculinization. The child is larger and appears more mature than normal; pubic hair may be profuse and body hair of adult male distribution. The clitoris may be enlarged and the voice low in pitch. There are, however, no breast development, no menses, no evidences of ovarian stimulation, and no evidence of endometrial or uterine maturity. Thus, it is in reality a pseudo pubertas precox. The same clinical picture may be seen in the presence of adrenocortical adenoma (Fig. 2).

Figure 2

Pseudo pubertas precox in a girl at the age of 3 years and 4 months. An adrenal adenoma was removed. The same patient at the age of 3 years and 8 months. It is interesting that regular menses appeared when she was 8 years of age.

Pseudo pubertas precox (of adrenal origin) must be differentiated from the physiologic type of pubertas precox arising from hypothalamic pituitary stimulation, which is characterized by increased amounts of urinary gonadotrophin, breast growth, endometrium typical of that which follows ovulation, and perhaps regular menses at a very early age.

The possibility of granulosa-cell tumor of the ovary must also be considered. By early and excessive estrogen production, such a tumor may cause all the evidences of true pubertas precox which are due to estrogen. Ovulation does not occur. However, the typical progestational changes in the endometrium do not occur. An endometrial biopsy may therefore produce the most important evidence in differential diagnosis.

Women with adrenogenital syndrome characteristically have large and extraordinarily strong bodies, increased body hair with male distribution, enlarged clitoris, and irregular or absent menses.

Osteoporosis is usually absent. Arterial hypertension and diabetes appear less frequently and usually in milder form than in Cushing's syndrome. There may be some Cushingoid features.

Clinically adrenogenital syndrome in women can be mimicked almost exactly by Stein-Leventhal syndrome (sclerocystic ovaries, "oyster" ovaries).

Pituitary hyperfunction from tumor has not been recognized clinically as a cause of adrenogenital syndrome despite the fact that it is well known that ACTH increases the androgen content of adrenal venous blood. This is apparently due to an enzymatic block.

In boys, adrenogenital syndrome produces pubertas precox, whether it begins in intrauterine life or later. The characteristics are large body size, heavy musculature, excessive penile growth, deep voice, increased body hair, and increased skeletal maturity. There is, however, no abnormal growth of the testes or early fertility. As in girls this is pseudo pubertas precox (Fig. 3). True pubertas precox is an abnormality in timing; in a boy one or two years old, gonadotrophins are measurable in the urine and may be within the range for normal adults. The testes are large. In a one-year-old boy, testicular development as shown by biopsy may simulate normal development for a newborn or at the beginning of puberty (Fig. 4), and active spermiogenesis may be present at four years of age.

Figure 3

Pseudo pubertas precox of adrenal origin. Testes normal size. At age 8 years and 9 months: height 60 inches; bone age 18 years; urinary 17-ketosteroids 30 mg. per 24 hr. At age 17 years: height 61¾ inches. Normal boy shown for comparison is 8 years and 10 months old, height 53 inches.

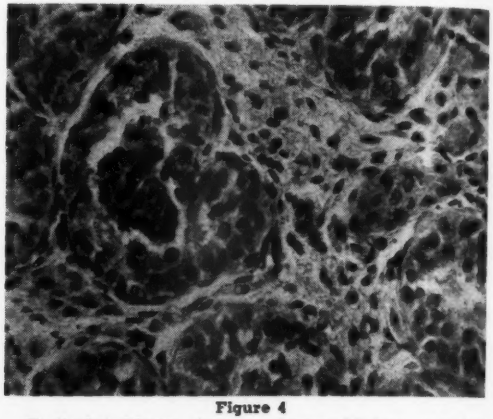


Figure 4

Testicular biopsy from a 1-year-old boy who had pubertas precox of the hypothalamic type. Testicular maturity is approximately normal for age 10 years. His urinary gonadotrophins were within the normal adult range; urinary 17-ketosteroids, 1.3 mg., and 17-hydroxycorticoids 1.9 mg. per 24 hr.

The urinary 17-ketosteroid values may approach adult normal values for that fraction which arises from precursors from the Leydig cells.

In some instances no organic lesions can be found in the hypothalamus. In some patients the syndrome may be associated with an infiltrating tumor in the region of the posterior hypothalamus and occasionally with a small hamartoma. Pneumoencephalography, electroencephalography, or ventriculography may be helpful in demonstrating a hypothalamic lesion. In each type of pubertas precox, if it is untreated, the epiphyseal lines close early. Growth is rapid at first, but eventually some degree of dwarfism occurs.

The treatment of adrenogenital syndrome consists of continued medical adrenal suppression or surgery. For hyperplasia, surgery seldom seems warranted. If it is, we advocate removal of one adrenal and three-fourths of the other, not total ablation. If a tumor is present it is removed if possible. Supportive therapy at the time of operation is not so important as in Cushing's syndrome, but doses of cortisone gradually diminishing from 200 mg. per day in adults (100 mg. per day in children) on the day of surgery to none in five or six days are usually used. A further postoperative ACTH test will give some assurance as to the functional capacity of remaining adrenal tissue.

In the physiologic variety of pubertas precox in boys, the administration of adrenal steroids or estrogens can be tried to suppress the pituitary

function. If the condition arises from a hypothalamic tumor, little suppressing effect of cortisone can be expected. It is well to remember that both adrenogenital syndrome and Cushing's syndrome may arise from adrenal rests which may be in the ovary or testis.

Idiopathic Hirsutism

Adrenal hyperactivity is involved in some cases of what formerly has been called idiopathic hirsutism. This condition probably should be considered a counterpart — or perhaps better — a mild form of adrenogenital syndrome. In women, increasing growth of hair in the male distribution is usually the only clinical evidence of abnormality, although oligomenorrhea may be present. Total urinary 17-ketosteroids are increased. In several of my patients they were increased to levels of 30 to 40 mg. per day. Robinson, Dimoline, and Jones[11] report a mean level of total urinary 17-ketosteroids of 24.0 mg. in six such patients. Their daily mean for urinary 3-beta ketosteroids was 5 mg. Normal controls had a mean of 9.6 mg. for 17-ketosteroids and 1.1 mg. for the 3-beta fraction. In most of these women adrenal surgery scarcely is warranted, though some of our patients, because of the nature of the symptoms and urinary 17-ketosteroids approaching 30 mg. per day, have undergone surgical exploration. Adrenal[12] suppression with hydrocortisone and more recently with prednisolone alone or in combination with 9-alpha fluorohydrocortisone over a long period of time may produce a striking regression of hair growth. Good results are inconstant. The condition must be differentiated from masculinizing ovarian tumors.

Cushing's Syndrome

Few instances of Cushing's syndrome are seen in the average physician's practice, but almost all physicians are acquainted with it as produced by large doses of cortisone or of its relatives given for pharmacologic effects in various diseases. My remarks here will be limited to a few aspects of diagnosis and treatment. As in many types of endocrine disease, the diagnosis in a typical, advanced case of Cushing's syndrome may be easy, but in less severe instances difficult. Tests are useful, but not infrequently clinical judgment based on experience remains the court of last resort.

The most helpful diagnostic feature in Cushing's syndrome is the deep red, round, full-moon face. There is nothing else which simulates it closely except perhaps the red face of a burly drayman. Other symptoms (Fig. 5) in approximate order of frequency include obesity of the trunk with an upper dorsal fat pad, arterial hypertension in about 80 per cent of patients, diabetes mellitus in approximately 75 per cent in our experience (31 of 40 patients), purple striae atrophica, ecchymoses, amenorrhea, asthenia, osteoporosis, marked thinning of the skin, and psychological changes or psychoses. Sometimes generalized convulsions occur, and when they do, xanthochromia of the spinal

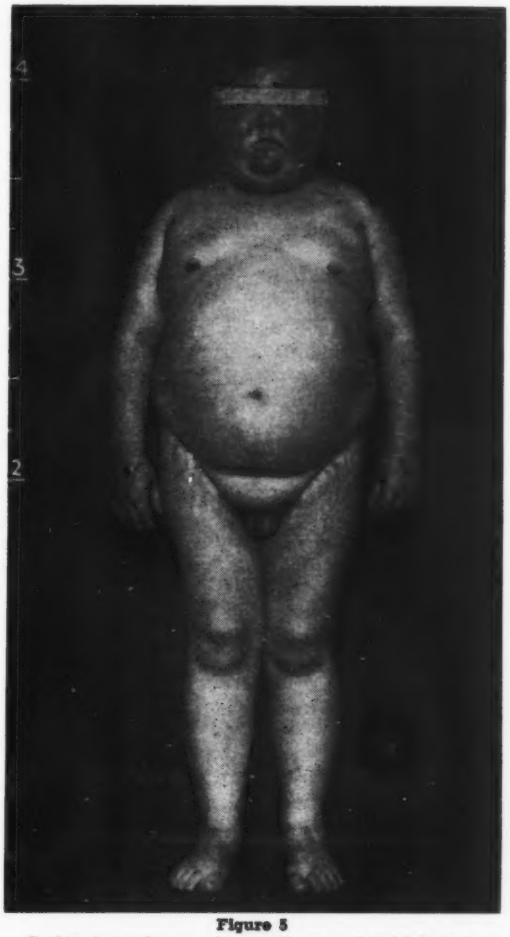


Figure 5

Cushing's syndrome. At age 11 years: height 52 inches; weight 119 pounds; urinary 17-ketosteroids 11.5 mg. per 24 hr. Adrenals were of normal size, and were not resected. Roentgen treatment, 2100 r to each temple at the skin, was administered.

fluid may be demonstrable. Virilization is given a highly prominent place in most descriptions of this disease. Actually it usually is present but mild, affecting chiefly the cheeks and lips which in most instances are covered with fine silky hair somewhat longer than normal.

Some degree of polycythemia is the rule. The blood sodium content may be rather high, that of chloride and of potassium slightly low, and in some patients, alkalosis is present. Roentgen findings often include a mottled appearance of the skull, and sometimes the decalcification of the clinoid processes due to osteoporosis may be mistaken for the effects of a pituitary tumor. Osteoporosis affects the spine more than it does the rest of the skeleton. Compression fractures of the vertebrae are common and may be the first symptom to cause alarm. Arterial hypertension in severe Cushing's syndrome

simulates that seen in malignant hypertension. General debility is often aggravated by various infections to which the body has low resistance. The mechanism of the hypertension is not entirely clear. The possibility of an excess of desoxycorticosterone and aldosterone must be considered. The hypertension does disappear completely in early cases that are cured. However, if the disease is of long standing all other evidences may vanish and most of the hypertension remain. Coronary occlusion is common.

In this disease, assays for urinary corticoids are almost always somewhat elevated, but in some typical instances the output is normal.

Results of attempts at suppression of adrenal activity are of approximately the same diagnostic value as results of stimulation. If high values of urinary corticoids can be reduced to 1 or 2 mg. per 24 hours within a few days on a course of 40-mg. doses of prednisolone or of 4-mg. doses of fluorohydrocortisone, hyperplasia is likely to be present. Some suppression occurs, however, in certain instances of proven adenoma or carcinoma. Examples of stimulation and suppression are shown in Figure 6.

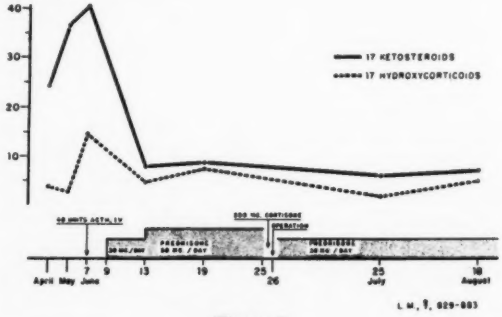


Figure 6

Stimulation and suppression of urinary steroids in adrenogenital syndrome with hyperplasia.

Pituitary tumor as a cause of Cushing's syndrome should be kept in mind, although it is rare; we have seen only two proven cases. Clinical Cushing's syndrome is seen also in primary thymic carcinoma, and sometimes in association with bronchogenic carcinoma.

In one of our patients with pituitary tumor and Cushing's syndrome, the pituitary tumor was found at necropsy. At the time we concluded the tumor to have antedated the Cushing's syndrome.

It has recently been suggested, however, that adrenal failure might lead to the production of a pituitary adenoma as in one instance in which very high blood levels of ACTH fell after removal of a pituitary adenoma in a patient who previously had been adrenalectomized.[13]

A new drug called amphenone has the power of producing marked adrenal suppression. In Cushing's syndrome amphenone given intravenously at a rate of 1 gm. per hour will suppress the plasma corticoids within a few hours from high to normal values. Doses of 0.5 gm. given orally every two hours will maintain blood pressure levels that were previously 180, at approximately 120 mm. Hg systolic. Alkalosis if present may disappear rapidly, and abnormally low potassium values will rise to normal. Diabetic status may be improved by this drug to the extent that insulin doses in the range of from 40 to 50 units can be discontinued, and blood sugar values will be maintained at normal.[14] Unfortunately amphenone is rather toxic and is not entirely suitable for clinical use.

Suppression of hormonal activity with fluorohydrocortisone has not yet been given a fair trial as treatment. Roentgen irradiation to the pituitary is still used by some physicians, and good results in the majority of patients treated are claimed by its advocates.[15]

The consensus, however, still is in favor of adrenal surgery. Excision of a tumor or removal of one adrenal and three-fourths of the other is the treatment of choice in our experience. However, because of rather frequent recurrences, bilateral total adrenalectomy is advocated by some experienced endocrinologists. My own preference is to risk a recurrence rather than to accept Addison's disease imposed upon a patient when it may be needless (Fig. 7).

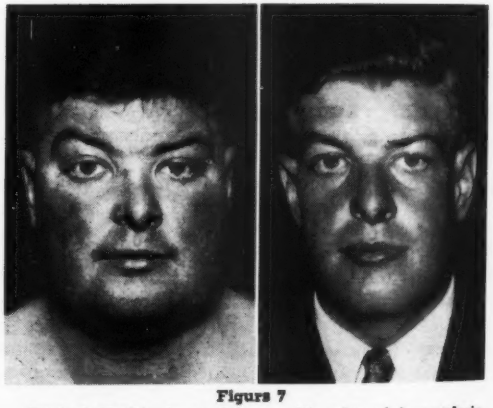


Figure 7

Typical Cushing's syndrome with adrenal hyperplasia. Complete remission except that the hypertension, although improved, did not disappear. One adrenal and four-fifths of the other were removed.

Before operation, large doses of cortisone usually are given, in the range of 200 to 300 mg. per day for two days; and smaller doses gradually diminished to 25 to 50 mg. per day in the following week. Withdrawal should be performed with great caution; where compensatory atrophy has occurred because of a tumor, it is not safe to assume that a good postoperative response to exogenous ACTH guarantees continued normal function.[16] The patient may respond well to exogenous ACTH but later lapse into adrenal deficiency.

Primary Aldosteronism

It has been known for many years that the amorphous fraction made from extracts of the adrenal glands, although impure, is capable of causing greater retention of sodium than that caused by desoxycorticosterone in dosages of the same weight, even though up to a few years ago desoxycorticosterone was the most powerful salt-retaining factor that had been identified chemically. This extremely active hormone in the amorphous fraction was known at first as electrocortin because of its effects on electrolytes; and subsequently when its origin was identified, it was named aldosterone.

The first case of primary aldosteronism was described by Conn.[17] Many investigators interested in endocrinology had been searching for this disease, believing that somewhere it must exist, but most were misled because animal experimentation with aldosterone was characterized chiefly by salt retention and edema. At the time we[18] reported our three patients with aldosterone-producing tumors, we were aware of 16 cases in the world literature. In February 1958, we knew of 63 such patients, and in September 1958, Conn knew of 108.

Primary aldosteronism is manifested usually by episodes of muscular paralysis. These may be mild or very severe, simulating familial periodic paralysis. In many of the patients there also is tetany associated with alkalosis, polyuria, arterial hypertension, imbalance of electrolytes, and inability of the kidneys to concentrate and acidify the urine. Diabetes of a mild type is common. A few cases have been studied for gastric acidity and were found to have marked hypoacidity which disappeared after cure of the disease. Edema is not a feature of primary aldosteronism, as it is in aldosteronism due to nephrosis, or cardiac or hepatic decompensation. Of 108 known cases the majority had adenoma, 10 per cent had hyperplastic glands, 6 per cent carcinoma, and 4 per cent were apparently normal.

The typical chemical findings in the blood are abnormally low levels of serum potassium, increased levels of serum sodium, and a tendency to alkalosis. The low serum potassium is associated with typical electrocardiographic changes. After surgical treatment, in our patients there was for a time a tendency to overcorrection of the electrolyte abnormalities with hyperkalemia and acidosis which spontaneously became corrected after several weeks. These assays in our cases were done by Dr. Gordon Farrell*, and the aldosterone was identified as aldosterone diacetate. Although our patients had fairly constant preoperative hypokalemia, this has not been true in all patients in the more recently published reports. Sometimes the serum potassium values have been normal repeatedly and abnormally low only occasionally. In each of our patients the symptoms disappeared promptly and completely after removal of the adenoma.

So far as the diabetes was concerned, in our own patients it amounted to little more than a suggestion in one, in another it disappeared completely as shown by the accompanying graph (Fig. 8), and in the third patient who was diabetic prior to the development of aldosteronism the diabetes was ameliorated—but did not disappear.

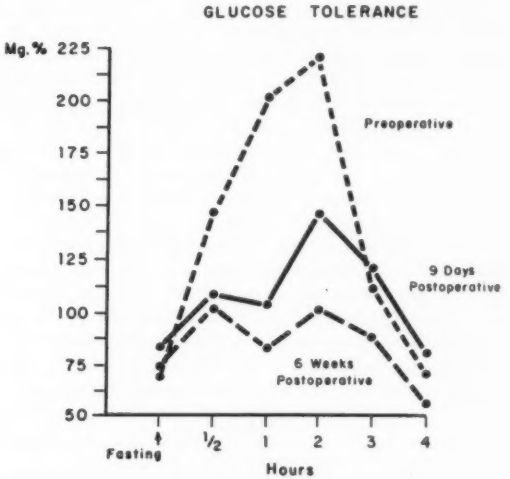


Figure 8

The inability of the kidneys to concentrate and acidify the urine properly, and the frequent presence of albuminuria and a few leukocytes and casts in the urine have led in the past to the diagnosis of "potassium-losing nephritis." Recently the condition diagnosed as potassium-losing nephritis has in some instances been shown to have been primary aldosteronism. In some patients, if the condition has not been severe or long-lasting, there is a complete reversal of the functional changes in the kidney. Renal efficiency in both acidification and concentrating power are improved postoperatively. In some in whom the disease has been prolonged and severe, there is permanent damage to the renal tubules, presumably due directly to the large amount of potassium in the filtrate and in a few instances glomerular damage has also been present. The characteristic microscopic renal lesion appears to be vacuolation of the tubular epithelium, focal parenchymal calcification, and arteriolarsclerosis.

Clinically the diagnosis usually is suspected on the basis of arterial hypertension with spells of weakness, and electrocardiographic changes that lead to a suspicion of low values of serum potassium. This combination then may lead to the discovery that the serum potassium value is actually low, and other findings then lead in turn to the proper diagnosis.

*Western Reserve University School of Medicine, Cleveland, Ohio.

It has been shown that in some instances periodic paralysis may be associated with intermittent aldosteronism. Appropriate studies have been described in such patients.[19] The episodes of paralysis are preceded by "large increases in urinary aldosterone and intense retention of sodium." Apparently at times episodes of paralysis may occur after strenuous exertion and thirst, especially if a great deal of salt and water are ingested. The serum potassium value is likely to become excessively low, although paralysis under these circumstances has been reported when potassium values are not sufficiently low to be considered abnormal. The paralysis may be controlled at the time of the acute attack by intravenous injection of potassium; and, in some instances, by the daily use of extra potassium orally over long periods of time, although episodes of paralysis have been known to occur even when as much as 12 gm. of potassium chloride is ingested daily. The condition may improve or disappear spontaneously. Low sodium intake is now being used in treatment and seems to be effective, but experience is not yet sufficient to warrant any statement as to its continued effectiveness. Diuretics, such as chlorothiazine (Duril), which lower serum sodium, will undoubtedly be tried and may prove useful.

References

1. Davis, J. O.: Some aspects of physiology of aldosterone. J.N.M.A., 49: 42-50, Jan., 1957.
2. Bartter, F. C., Mills, I. H., Biglieri, E. G. and Delea, C. S.: Studies on control of physiologic action of aldosterone. Laurention Hormone Conference Inc., Program, Sept. 7-12, 1958.
3. McCally, M., Anderson, C. H. and Farrell, G. L.: Effects of atrial stretching on aldosterone secretion. Endocrine Society Program, Abstract No. 184, June, 1958.
4. Farrell, G. L., Fleming, R. B., Rauschkolb, E. W., Yatsu, F. M., McCally, M., and Anderson, C. H.: Steroidogenic properties of purified corticotropins. Endocrinology, 62: 506-512, April, 1958.
5. Symington, T., Currie, A. R., O'Donnell, V. J.; Grant, J. K., Oastler, E. G. and Whyte, W. G.: Hyperplasia and tumours of the human adrenal cortex: histology, enzymic changes and corticoid production. In Ciba Foundation Colloquia on Endocrinology 12: 101-121, 1958.
6. Dorfman, R. I. and Shipley, R. A.: Androgens; Biochemistry, Physiology, and Clinical Significance. New York: John Wiley & Sons, Inc., 1956, 590 pp., p. 15.
7. Romanoff, E. B., Hudson, P. B. and Pincus, G.: Isolation of hydrocortisone and corticosterone from human adrenal vein blood. J. Clin. Endocrinol., 13: 1546-1548, Dec., 1953.
8. Schiller, S., Miller, A. M., Dorfman, R. I., Sevringhaus, E. L. and McCullagh, E. P.: Metabolism of steroid hormones: isolation of Δ 5-androstenediol-3 (beta), 17 (alpha) and Δ 5-pregnenediol-3 (beta), 20 (alpha). Endocrinology, 37: 322, 1945.
9. Gallagher, T. F.: On alterations in adrenal function, especially with adrenocortical carcinoma. Cancer Res., 17: 520-529, June, 1957.
10. Wilkins, L., Jones, H. W., Jr., Holman, G. H. and Stempfel, S. R., Jr.: Masculinization of female fetus associated with administration of oral and intramuscular progestine during gestation. Endocrine Society Program, Abstract No. 60, June, 1958.
11. Robinson, Alice M., Dimoline, Ann and Jones, Dora G.: Consideration of some types of adrenal tumours. In Ciba Foundation Colloquia on Endocrinology, 12: 135-152, 1958.
12. Perloff, W. H., Channick, B. J., Suplick, B. and Carrington, Elsie R.: Clinical management of idiopathic hirsutism (adrenal virilism). J.A.M.A., 167: 2041-2047. Aug. 23, 1958.
13. Nelson, D. H., Meakin, J. W., Dealy, J. B., Jr., Matson, D. D., Emerson, K., Jr. and Thorn, G. W.: ACTH-producing tumor of pituitary gland. New England J. Med., 259: 161-164, July 24, 1958.
14. McCullagh, E. P. and Tretbar, H. A.: Treatment of Cushing's syndrome with amphenone: report of two cases, one with probable thymoma. J. Clin. Endocrinol., 18: 134-148, Feb., 1958.
15. Dohan, F. C., Raventos, A., Boucot, N. and Rose, E.: Roentgen therapy in Cushing's syndrome without adrenocortical tumor. J. Clin. Endocrinol., 17: 8-32, Jan., 1957.
16. Kyle, L. H., Meyer, R. J. and Canary, J. J.: Mechanism of adrenal atrophy in Cushing's syndrome due to adrenal tumor. New England J. Med., 257: 57-61, 1957.
17. Conn, J. W.: Presidential address painting background; primary aldosteronism, new clinical syndrome. J. Lab. & Clin. Med., 45: 3-17, Jan., 1955.
18. Hewlett, J. S., McCullagh, E. P., Farrell, G. L., Dustan, Harriet P., Poutasse, E. F. and Proudfit, W. L.: Aldosterone-producing tumors of the adrenal gland: report of three cases. J.A.M.A., 164: 719-726, 1957.
19. Conn, J. W., Louis, L. H., Fajans, S. S., Streeten, D. H. and Johnson, R. D.: Dependence of attacks of periodic paralysis upon retention of sodium; and failure to induce either paralysis or sequestration of potassium when dietary sodium is restricted. Tr. A. Am. Physicians, 70: 167-182, 1957.

The Recognition and Management of Renal Hypertension

D. D. Gellman, M.D., (London), M.R.C.P.

In the decade following the experimental production of hypertension in animals by partial occlusion of one or both renal arteries[3] many patients with hypertension and unilateral renal disease were subjected to nephrectomy. However, enthusiasm for this form of treatment waned when it was realized that the hypertension was not usually benefited. In a review of published records, Homer Smith[10] found that in only one quarter was the blood pressure restored to normal. In earlier series the success rate was even less, ranging from nine per cent[4] to nineteen per cent[9]. This was not really surprising, since the pathological conditions most commonly found — chronic pyelonephritis, pyonephrosis, and tuberculosis — bore no resemblance to the experimental "Goldblatt kidney."

Recently there have been an increasing number of reports of patients in whom hypertension was apparently caused by the exact counterpart of the Goldblatt experiment, viz; partial obstruction of one or both renal arteries. The importance of these cases is threefold. First, they are not so uncommon as was once supposed. In 1957 the writer[2] was able to collect 31 cases from the literature. Since then reports of a further 15 cases have been published, and a further 20 or more reported at meetings. Second, it seems that, if the condition is recognized sufficiently early, a very high proportion of these patients can be relieved of hypertension permanently[2]. Third, the study of these patients has helped to clarify the general problem of the investigation and management of renal hypertension. It is this latter aspect which will be dealt with in the present paper.

Division of Medicine, The Winnipeg Clinic.

The Selection of Patients for Intensive Investigation

It is a reasonable generalization that any case of hypertension that is severe enough to require treatment also requires some investigation. This should begin with a careful urinalysis, estimation of the blood urea nitrogen (B.U.N.) or serum creatinine, and intravenous pyelography (I.V.P.). On the basis of the results of the I.V.P. patients may be divided into four groups:

(1) Those in whom both kidneys concentrate the dye poorly or not at all.

(2) Those in whom the dye is not concentrated at all by one kidney, the other being apparently normal.

(3) Those in whom the difference between the two kidneys is more subtle, i.e., one kidney is smaller than its fellow, or concentrates the dye less well, or with some delay.

(4) Those in whom both kidneys have equal, and apparently normal, function.

Groups 1 and 2 present little problem. When bilateral renal disease is present, hypertension must be treated by purely "medical" means, except in the rare case when a healthy identical twin is prepared to donate a kidney[6]. When one kidney is completely functionless there will usually be a definite surgical indication for its removal, and relief of hypertension may be an additional benefit. In any case, if the function of the other kidney is normal, there is nothing to be lost by removing the non-functioning one. However, if the non-functioning kidney is of normal size a needle biopsy should be taken from it before operation. If it proves to be histologically almost normal, aortography should be performed, since if (as is likely under these circumstances) a lesion of the main renal artery is found, it may be possible to restore function to the kidney by a suitable grafting operation[8].

Patients in group 3 will usually require further investigation, since one hesitates to remove a functioning kidney unless the indications are quite clear-cut. Two questions must be answered. First, is the abnormal kidney the cause of the hypertension or merely a coincidental finding? Second, if one kidney was the original cause of the hypertension, has the contralateral kidney been so damaged that it too is now contributing to the hypertension? Under these circumstances, removal of the frankly abnormal kidney will not only fail to relieve the high blood pressure (as was shown by Wilson and Byrom[13] in their studies on rats) but may even be detrimental to the patient's survival, if the function of the remaining kidney is insufficient to maintain homeostasis. The answer to this second question may be immediately obvious if the patient has severe azotaemia, and the answer to the first question then becomes academic. If, however, in patients classified as group 3 on the basis of the I.V.P., the B.U.N. or serum creatinine is normal or only slightly raised, then the investigations discussed below should be carried out.

It is in patients in group 4 that the decision regarding more intensive investigation may be most difficult. Certainly, a normal I.V.P. does not exclude a renal artery lesion as the cause of hypertension. In a series of 31 patients in whom a unilateral renal artery lesion was demonstrated and whose hypertension was relieved by nephrectomy, no less than five (16%) had completely normal I.V.P.s and a further three (10%) had only slight reduction in the size of one kidney which was overlooked on first examination[2]. In the presence of a normal I.V.P. the investigations discussed below are indicated in the following:

A. Young patients with no family history of, and no apparent cause (such as nephritis, coarctation of the aorta, phaeochromocytoma, primary aldosteronism, etc.) for, hypertension.

B. Elderly patients with sudden onset of "accelerated" hypertension.

C. Patients with essential "benign" hypertension whose disease suddenly "accelerates," especially when this "acceleration" follows an attack of unexplained pain in the abdomen or flank, or abdominal injuries or operation. Such an episode had occurred in 18 of a series of 31 patients with renal artery lesions[2].

Further Investigations

As outlined above, the clinical findings and results of simple investigations enable the physician to select those hypertensive patients in whom further studies of the renal blood supply are indicated. There are two main approaches, each of which has its ardent proponents.

(a) Renal Handling of Sodium and Water

White[12] has shown experimentally in dogs that gradual occlusion of one renal artery results in the production of a smaller urine volume, with a lower concentration of sodium, by the affected kidney, before any fall in inulin and P.A.H. clearances can be demonstrated. Connor, Berthrong, Thomas and Howard[1] have applied this finding to the detection of unilateral renal ischaemia in man. Essentially the investigation involves catheterization of the ureters and the collection of simultaneous specimens of urine from the two kidneys for two or more periods of about 45 minutes. In practice, if the results are to mean anything, the test must be carried out with the minutest attention to detail, and readers are advised to study the relevant parts of Connor's paper very carefully before attempting this investigation. In the writer's experience it rarely takes less than three hours for the whole procedure to be completed satisfactorily, so that it represents a considerable trial for the patient.

Even when the test has been satisfactorily carried out, the interpretation may be difficult. A positive result — i.e., one kidney excretes a smaller volume of urine, with a lower sodium concentration, than

its fellow — certainly suggests that the kidney is affected by an ischaemic process and that relief of hypertension will follow its removal (if the contralateral kidney has not been damaged). However, a negative result — i.e., no significant difference in the excretion of water and sodium on the two sides — doses not necessarily exclude a remediable renal lesion as the cause of hypertension. Cases have been described in which stenosis of renal arteries on *both sides* was present and hypertension was relieved by the grafting of both renal arteries[8]. Such a case would be overlooked by an investigation which depends essentially upon a *comparison* of the two kidneys. Probably less rare is hypertension due to obstruction of an anomalous renal artery or a branch of a renal artery. Under these circumstances the mass of ischaemic kidney tissue may be so small that sodium handling is not affected and the test would give a negative result.

Despite these criticisms, this test has a definite place in the investigation of renal hypertension, particularly when facilities for aortography are not available. It should carry none of the risks which are sometimes attendant on aortography. The information it yields can be increased if blood samples are taken during the periods of urine collection. If this is done the clearances of urea and creatinine can be calculated for each kidney, thus providing a valuable measure of the function of the "good" kidney.

(b) Abdominal Aortography

Renal handling of sodium and water is, at best, only an indirect method of studying renal blood flow. By contrast, abdominal aortography enables one to see the state of the renal arteries and their branches directly. Furthermore, interpretation of the findings does not depend upon comparison of the two sides; abnormalities of the blood supply of both kidneys can be detected.

Although a number of serious misadventures following aortography have been reported[5] the overall mortality and morbidity are not high in relation to the seriousness of progressive renal hypertension. In experienced hands the procedure is safe, provided certain precautions are taken[7]. If the blood pressure is excessively high, it should be lowered by the intravenous injection of a hypotensive drug. The tip of the needle should be aimed to enter the aorta at about the level of the lower half of the first lumbar vertebrae; this will be at, or just below, the origin of the renal arteries. If the dye is injected above the origin of the renal arteries some escapes into the coeliac axis and obscures the view of the renal arteries. Most of the mishaps of aortography have been due to injection of concentrated dye directly into a renal artery or into the wall of the aorta. This can be avoided by taking preliminary films using a small quantity of dilute opaque media. Once the needle is correctly positioned, 10 c.c of 50% Hypaque should be injected as quickly as possible. If a rapid cassette changer is not available the exposure should be made as the last few cubic centimeters of dye are being injected. The timing of the exposure is most important. The film should be developed at once and the procedure repeated if necessary.

With these precautions no serious complications were encountered in a series of over 400 abdominal aortograms, three-quarters of them in patients with hypertension[7].

(c) Direct Measurement of Renal Blood Flow

Recently, methods have been developed for the measurement of renal blood flow using radioactive Diodrast and external scintillation counters[11]. At first sight this would seem to be the ideal method for the investigation of renal hypertension. However, the method cannot distinguish between impaired blood flow due to primary renal artery obstruction, and the reduced blood flow which may accompany any chronic renal disease. Furthermore, in those cases which present the greatest diagnostic problem (Group 4) the abnormality seems to be a damping of the pulse pressure in one kidney rather than a gross diminution of blood flow. Measurement of renal blood flow with radioactive Diodrast is therefore unlikely to contribute much to the investigation of renal hypertension.

Management

The results of ureteric catheterisation studies and abdominal aortography should indicate whether one kidney is responsible for hypertension and whether the contralateral kidney is functioning sufficiently well to maintain homeostasis by itself. Both these investigations should always be carried out before an operation is performed on a *functioning* kidney for the relief of hypertension

If surgery is decided upon, a choice must be made between nephrectomy, and restoration of the renal blood supply. If the primary abnormality is renal artery obstruction, and if the aortogram shows that there is normal renal artery distal to the obstruction, the possibility of inserting a renal artery homograft should be seriously considered. In making the decision, valuable additional information may be obtained by percutaneous needle biopsy of the kidney. Thus, if the offending kidney is histologically normal, every attempt should be made to restore its function by restoring its blood supply. On the other hand, if established intrinsic disease or severe fibrosis is found in a biopsy of the offending kidney, there is no point in attempting a grafting operation even if a study of the aortogram suggests that it might be technically possible. Nephrectomy is the operation of choice in these circumstances.

Unfortunately, in the majority of patients with renal hypertension the kidney disease is either bilateral from the beginning, or has become so by

the time the patient comes to his physician. However, it is important to bear in mind the possibility of remediable kidney disease in any patient who has hypertension that is in any way unusual, since a radical cure is often possible. The management of those patients whose renal disease is not amenable to surgery is similar to that of patients with "essential" hypertension, though one must be constantly aware of the risks of accentuating renal insufficiency by too rapid a reduction of blood pressure or too vigorous depletion of sodium.

References

1. Connor, T. B., Berthrong, M., Thomas, W. C. and Howard, J. E. (1957): Hypertension due to unilateral renal disease — with a report on a functional test useful in diagnosis. Bul. Johns Hopk. Hosp., 100: 241.
2. Gellman, D. D. (1958): Reversible hypertension and unilateral renal artery disease. Quart. J. Med. N.S., 27: 103.
3. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W. (1934): Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischaemia. J. Exp. Med., 59: 347.
4. Goldring, W. and Chasis, H. (1944): Hypertension and hypertensive disease, New York. The Commonwealth Fund.
5. McAfee, J. G. (1957): A survey of complications of abdominal aortography. Radiology, 68: 825.
6. Murray, J. E., Merrill, J. P. and Harrison, J. H. (1958): Kidney transplantation between seven pairs of identical twins. Ann. Surg., 148: 343.
7. Poutasse, E. F. (1958): Personal communication.
8. Poutasse, E. F., Humphries, A. W., McCormack, L. J. and Corcoran, A. C. (1956): Bilateral stenosis of renal arteries and hypertension: treatment by arterial homografts. J.A.M.A., 161: 419.
9. Smith, H. W. (1948): Hypertension and urological disease. Amer. J. Med., 4: 724.
10. Smith, H. W. (1956): Unilateral nephrectomy in hypertensive disease. J. Urol., 76: 685.
11. Taplin, G. V., Meredith, O. M., Kade, H. and Winter, C. C. (1956): The radioisotope renogram. J. Lab. Clin. Med., 48: 886.
12. White, H. L. (1950): The excretion of sodium in relation to glomerular filtration. In Transactions of the second conference on Renal Function. Josiah Macy, Jr., Foundation. New York.
13. Wilson, C. and Byron, F. B. (1941). The vicious circle in chronic Bright's disease. Quart. J. Med. N.S., 10: 65.

Pathology

A Case of Wegener's Granulomatosis*

M. Van Wijhe, M.D.

"Wegener's granulomatosis" is one of the more uncommon conditions listed under collagen diseases. The first description is by Klinger[1] in 1931 and it was recognized by Wegener[2] in 1936 as a pathological entity.

The characteristic features are: necrotizing granulomas in the respiratory tract, necrotizing vasculitis involving both arteries and veins and glomerulonephritis. The latter develops in the later stages of the disease and in the majority of cases is the final cause of death. Because of the relative rarity of the condition and the rather typical pathological picture our patient presented, it seemed worthwhile to report this case.

History

A 33 year old white man was healthy until February, 1958, at which time he had two right lower molar teeth extracted. Since then he noticed general malaise with fever and spent most of the time in bed. He also developed muscular aches, especially in both arms. The joints were painful but not swollen. His appetite was satisfactory and he did not lose weight.

Previous Illnesses

Tonsillectomy and adenoidectomy.
Scarlet fever.
Wrist fracture.

Physical Examination

He was admitted on May 22, 1958.

The patient was a pale, well-built man in no apparent distress. The heart was of normal size and revealed no murmurs. The pulse was regular at 124 per minute, blood pressure was 120/80 and temperature was 100.8°F.

A soft nodule was palpable in the right thyroid lobe. No abnormalities were noted in the lungs, either on percussion or auscultation. The liver and spleen were not palpable. No lymphadenopathy was noted. The extremities revealed no edema. Neurological examination was negative.

Laboratory Investigation

Hemoglobin 90% (14.3 grams), RBC 5,000,000, hematocrit 45%, total WBC 10,400. Differential: polys 77%, band 2%, eosinophils 1%, lymphocytes 10%, monocytes 10%. Platelets present. No L.E. cells noted. Sedimentation rate 45 mm. (first hour). Blood urea 12 mgm.%.

Urinalysis: specific gravity 1,030, sugar negative, protein ++ (0.1 gm.%). Sediment: 5-10 leukocytes, 200-300 erythrocytes, occasional granular casts. No agglutination titres were present for typhoid "O," typhoid "H," paratyphoid A and B or brucellosis. Blood culture was negative.

A urine culture displayed saprophytic micrococcus, sensitive to all of the antibiotics, except tetracycline and oxytetracycline.

X-rays taken of the chest showed multiple oval densities throughout the right lower lung field in the immediate supradiaphragmatic region and a large oval density, measuring three to four centimeters in diameter in the left costophrenic region. It was the impression that these lesions were compatible with metastatic deposits.

The heart and greater vessels appeared within normal limits.

An intravenous pyelogram showed a good functioning, rather large right kidney; no left kidney was visualized. X-rays of the mandible and sinuses were also done, but no abnormalities were noted.

*From the Department of Pathology, St. Boniface Hospital, St. Boniface.

A tentative diagnosis of septicemia was made and the patient was placed on a high dose of signemycin (500 mg. o.h. xii, intravenously).

Follow Up in Hospital

The patient did poorly and showed no improvement whatsoever. His fever continued high, ranging between 98° and 101°, with peaks up to 103°F. Occasional minor nosebleeds were noted. Repeated chest x-rays showed the lung densities unaltered.

An electrocardiogram suggested infarction of the lungs. On June 4, 1958, his blood urea had risen to 114 mg.%. The urine still contained protein and the sediment revealed leukocytes and abundant erythrocytes. The urinary tract infection had cleared following antibiotic therapy.

No Bence-Jones proteins were present. Blood proteins: total 5.2 gm.% (albumin 3.2 gm.%, globulin 2.0 gm.%). Electrolytes: potassium 4.9 mg./litre, sodium 132 mg./litre, chloride 92 mg./litre, CO_2 combining power 20 mm./litre. Repeated blood cultures were negative.

Hemoglobin 11.6 gm. (79%), total WBC 26,300, differential: polys 68%, band 19%, meta 1%, lymphocytes 9%, disintegrated 3%.

In view of the radiological findings a cystoscopy was performed which revealed no left ureteric orifice, suggesting congenital absence of the left kidney and ureter.

The patient progressively deteriorated and died on June 8, 1958, seventeen days after admission.

Treatment consisted of signemycin, 500 mgm., later replaced by mysteclin and neomycin, vitamins and analgesics.

Autopsy

Gross Description

The post-mortem was performed twenty-one hours after death. The body was in a fair nutritional state and the most significant findings were limited to the lungs, spleen and kidney.

The right pleural cavity contained 350 cc. of a sanguinous fluid and a fibrinous exudate was present over the pleural surface. Hard, nodular areas, measuring up to 2.0 x 2.0 x 3.0 cm. were present in both lower lobes, predominantly in the peripheral regions. (Fig. 1.) The cut surface revealed a cheesy appearance. Many middle-sized branches of the pulmonary artery were occluded by thrombi, in areas being associated with hemorrhagic infarction of the pulmonary parenchyma.

The trachea and major bronchi contained a purulent sanguinolent exudate; the mucosa appeared to be swollen and focally ulcerated.

The spleen weighed 205 grams. The normal architecture had completely disappeared, as the red pulp was replaced by irregularly-shaped foci of necrosis. (Fig. 2.) The splenic vein was occluded by a thrombus.

Congenital absence of the left kidney and ureter was confirmed.

The right kidney weighed 630 grams. Numerous fine petechiae were present over the surface and on cut section the cortex appeared to be markedly swollen and pale. It measured 1.5 cm. in thickness.

Microscopic Description

The caseous areas in the lungs showed a granulomatous inflammatory process with widespread coagulation necrosis and destruction of lung parenchyma. Marked proliferation of fibroblasts surrounded these areas of necrosis and was associated with formation of multinucleated giant cells, the latter being either of Langhans or foreign body type. (Fig. 3.) A cellular infiltrate predominantly composed of lymphocytes and plasma cells was added to this proliferative reaction. Polymorphonuclear leukocytes were limited to the necrotic areas. Eosinophilic cells were only occasionally noted. The necrotic regions showed in areas small central cavities. Similar granulomas were present in the bronchial mucosa, causing ulceration or squamous metaplasia of the overlying epithelium. (Fig. 4.) The bronchial involvement seemed to increase as the caliber became smaller (Fig. 5.), and apparently endobronchial spread and confluence resulted in the formation of the mentioned large caseous areas. The pulmonary arteries and veins showed extensive fibrinoid necrosis of their walls. (Fig. 6.) Middle-sized and smaller vessels were equally involved. This process was either diffuse or nodular in type and associated with thrombosis of the lumen. The remaining lung parenchyma showed interstitial pneumonitis with focal metaplasia of alveolar epithelium.

Multiple small granulomas were also noted in the mediastinal lymph nodes without destruction of the lymph node architecture. Epithelioid reticulum cells were the main constituents and necrosis in these granulomas was less pronounced.

The spleen showed massive acute fibrinoid necrosis of the trabecular arteries with recent thrombi occluding the lumina. The red pulp was replaced by a partially necrotic granulomatous inflammatory tissue, similar in appearance to the process described for the lung.

Acute necrotizing arteritis was also noted in the subserosal layer of the gall bladder.

The kidney showed diffuse glomerulonephritis. The glomeruli were swollen and displayed marked proliferation of endothelium and capsular epithelium. The capillary loops showed focal fibrinoid necrosis. (Fig. 7.) Cellular exudation was not prominent. Many glomeruli showed crescent formation, with giant cells presumably arising from the capsular epithelium (Fig. 8.) No periglomerular granulomata were noted. Many of the renal tubules were filled with erythrocytes and degenerative changes were seen in the lining epithelium.

The findings in the other organs were not contributory.

Pathological Diagnosis

Necrotizing granulomatosis of lungs and spleen with necrotizing angiitis and subacute glomerulo-

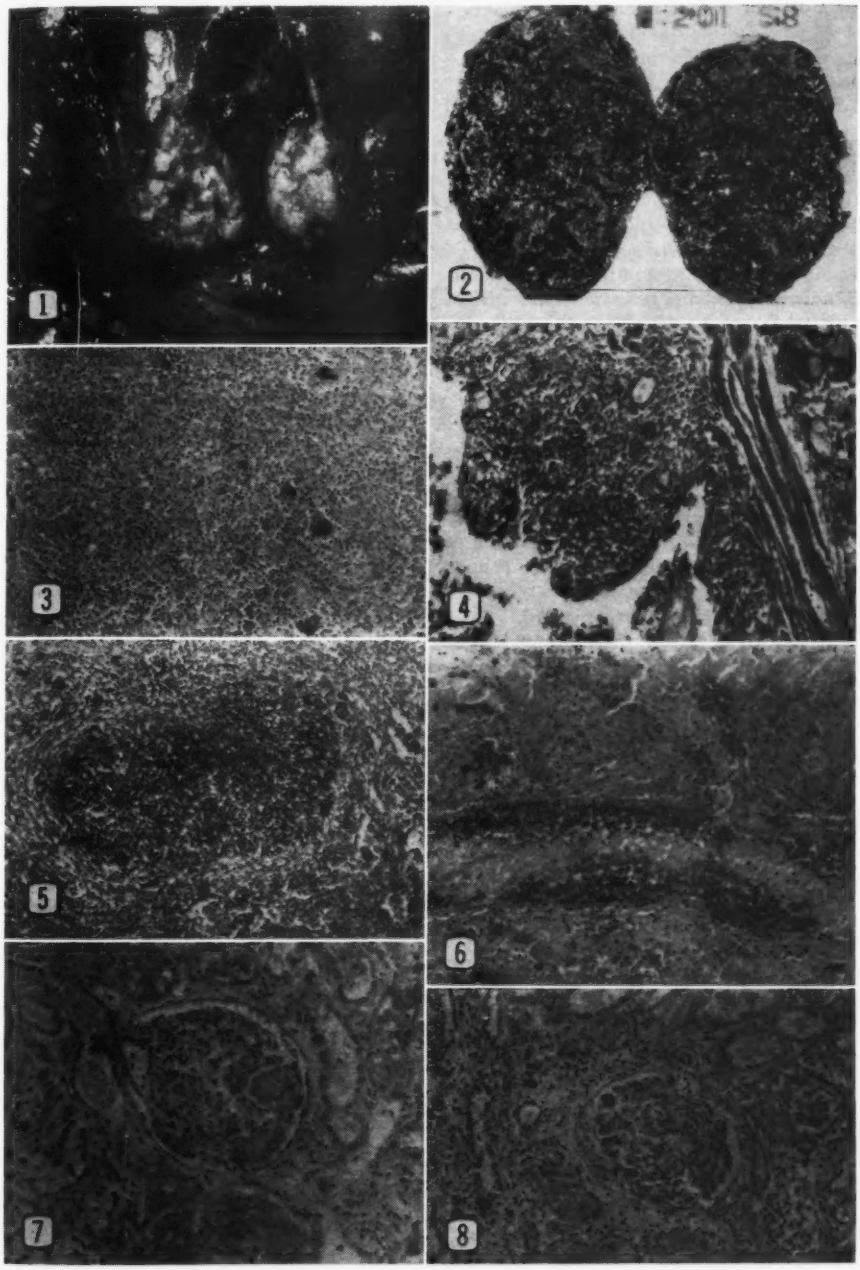


Fig. 1. Caseous granuloma in left lower lobe. **Fig. 2.** Cut section of spleen showing gyriform areas of necrosis and complete destruction of the normal architecture. **Fig. 3.** Granulomatous inflammation in lung with formation of multinucleated giant cells. (Haem. Eos. stain x 110). **Fig. 4.** Granuloma formation in mucosa of major bronchus. The surface epithelium is degenerated or has disappeared. (Haem. Eos. stain x 130). **Fig. 5.** More or less circumscribed granuloma with central necrosis. This probably represents an involved and completely destroyed bronchiolus. (Haem. Eos. stain x 110). **Fig. 6.** Acute necrotizing vasculitis with swelling of the wall and acute cellular infiltration. (Haem. Eos. stain x 110). **Fig. 7.** Fibrinoid necrosis of glomerular loops. (Haem. Eos. stain x 200). **Fig. 8.** Subacute glomerulonephritis with formation of multinucleated giant cells in Bowman's capsule. The convoluted tubules are distended and contain erythrocytes. (Haem. Eos. stain x 220).

nephritis, compatible with Wegener's granulomatosis.

Discussion

The disease has no predilection for men or women and usually appears in mid-life, although a case of a 12 year old girl has been reported (Godman[3]). The course is almost invariably fatal and runs about 3-4 months. Three of the five cases recently described by Hood[4] et al were asymptomatic and even showed radiologically complete clearing of the lung infiltrates. The diagnosis was established by lung biopsy. The histologic description of the lesion however, seems more compatible with Loeffler's syndrome, a disease which is known to run a benign clinical course.

The three fundamental lesions in Wegener's granulomatosis as already mentioned are:

1. Necrotizing granulomatosis of the respiratory tract.
2. Necrotizing vasculitis.
3. Glomerulonephritis.

1. Frequently the first evidence of the disease is an intractable rhinitis or sinusitis, together with the development of persistent cough, hemoptysis and perhaps chest pain. This is associated with symptoms of generalized malaise, unexplained fever, muscle and joint pain. The latter symptoms dominated in our patient.

Laboratory data is not contributory as to the diagnosis. A high sedimentation rate is usually present however, and the peripheral blood shows leukocytosis. Eosinophilia is not common. An allergic history is often absent.

The respiratory tract symptoms are explained by a peculiar type of chronic granulomatous inflammation and a biopsy from the nasal mucosa may be helpful in making the diagnosis.

When the lesions are restricted to the nose and pharynx, the distinction from granuloma gangrenescens is difficult. Neuss[5], in a recent article thinks it possible that both conditions are closely related and are members of the rheumatic diseases. This impression is strengthened by reported cases which showed ulcerative and granulomatous lesions of the nose, with bone necrosis and finally marked malformation of the face. Autopsies performed on some of these patients revealed involvement of the lungs and a chronic glomerulonephritis (Woodburn[6]). Although cases are described in which the lungs were not affected (Lindsay[7]), the lungs are almost invariably involved in the early phase of the disease. The lesions are wedge-shaped and frequently located in the peripheral portions of the lungs for reasons above mentioned. All authors report negative cultures for pathogenic bacteria and fungi. Throughout the bronchial tree a granulomatous and ulcerative process is noted in the mucosa, with exudation into the lumen. The smaller bronchi become obstructed and endobronchial extension finally completely replaced the involved lung segment with granulation tissue. The majority of these foci are present in the lower lobes. Clinically and radiologically the lesions are often mistaken for tuberculosis, abscesses or metastatic tumor. Many authors report an exploratory thoracotomy (Tuhy[8], Fienberg[9], Chomet[10]).

2. This granulomatous process is, in true Wegener's disease, associated with a necrotizing vasculitis, involving both the arteries and veins. Hemorrhagic infarctions following thrombosis of vessels are common. The vasculitis is of a fibrinoid degenerative type, similar to that observed in polyarteritis nodosa and allied diseases. Arteries of small caliber as well as medium-sized vessels are involved. We could not confirm the impression of Chomet[10] that only blood vessels within necrotizing granulomas were affected. Blood vessels outside granulomata were also involved and the finding of necrotizing vasculitis in the wall of the gall bladder suggests a disseminated pattern.

In discussing the vascular changes one meets transition to polyarteritis nodosa. The lungs in polyarteritis nodosa are not so seldom affected as was formerly thought. Rose [11] gathered 111 cases of polyarteritis nodosa and found the lungs involved in 28%. Sweeney[12] mentions a similar figure and both authors described a high (83) percentage with associated granulomatous lesions in the pulmonary parenchyma. Sandler[13] recorded a 39 year old man with polyarteritis and pulmonary cavitation. Thirty-five cases of "respiratory granulomatosis with polyarteritis nodosa (Wegener's syndrome)" were collected by Plumer[14] and he added two patients of his own. The author considers Wegener's granulomatosis as a subgroup of polyarteritis nodosa.

The differential diagnosis in respect to the pulmonary lesions also include Loeffler's syndrome, allergic angiitis and granulomatosis or chronic pneumonitis of cholesterol type (Fienberg[15]).

Godman and Churg[3] presented a detailed discussion on this subject.

Transitions from one form to another are regularly reported in literature and the impression is gained that the entire spectrum of mentioned diseases is related, or at least has a similar etiology.

3. Another important feature of Wegener's disease is glomerulonephritis. This does not manifest itself until midway or later in the disease and is in approximately 85% of the cases the cause of death.

The characteristic pathologic picture is that of a focal necrotizing glomerulitis, also seen in subacute bacterial endocarditis and polyarteritis nodosa. The necrosis is fibrinoid in nature and can involve large portions of the glomerulus. The reparative phase is characterized by proliferation of endothelium and crescent formation. Our case appeared to be in the subacute phase. Multinucleated giant

cells lying loose in Bowman's capsule were noted in many sections. They are probably also derived from capsular endothelium. We did not see granulomatous lesions in the periglomerular regions, as mentioned by Godman and Churg[3], and Fahey[16]. A case has been described by Weinberg[17] showing no disturbance of kidney function; glomerulonephritis, however, was demonstrated at autopsy.

Lesions in other organs are less common. Skin lesions are described by Walton[18] et al and Ahlstrom[19] et al. One of the cases reported by Tuhy[8] showed an unexpected involvement of the cerebellum. Granulomatous lesions are furthermore reported in the liver (Chomet[10]), lymph nodes, heart, joints and genitalia.

Therapeutic measures in Wegener's granulomatosis are disappointing. Cortisone treatment may cause remission. One patient described by Godman[3] and another by Fahey[16] received cortisone and was still alive three years after the onset of symptoms.

The placement of Wegener's granulomatosis in the nosological system is usually in the group known as diseases of hypersensitivity. As in many of these human hypersensitivity conditions, no antigen can be traced and no antibodies are demonstrable, the classification relying for the greatest part on morphological changes. These changes, depending on the severity and nature of the hypersensitivity, vary from tissue hyperemia and edema to fibrinoid or hemorrhagic necrosis, granuloma formation being most frequently seen in the tuberculin type of hypersensitivity.

On the basis of these criteria and excluding the other possible etiological factors, it seems a good possibility that Wegener's granulomatosis is a manifestation of hypersensitivity, although one has to remember that even the morphological changes are not specific.

Summary

A case of Wegener's granulomatosis is presented. The clinical and pathological findings are described and discussed in respect to other cases presented in literature.

Acknowledgment

The author gratefully acknowledges permission of Dr. S. S. Peikoff to present this case and to thank Mr. L. V. Stanford for the preparation of photographic material.

Bibliography

1. Klinger, H.: Grenzformen der Periarteritis nodosa. Frankfurter Ztschr. f. Path., 42: 455-480, 1931.
2. Wegener, F.: Uber eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung der Arteriensystems und der Nieren. Beitr. z. path. Anat. u. z. Allg. Path., 102: 36-68, 1939.
3. Godman, G. C., Churg, J.: Wegener's Granulomatosis. Arch. Pathol., 58: 533-553, 1954.
4. Hood, R. M., O'Connell, H. V., McCord, D. L.: Pathergic Granulomatosis (Wegener's Granuloma) of the Lung. Am. Rev. Tuberc., 78: 21, 1958.
5. Neuss, V.: Granuloma Gangraenescens (Wegener's Granulomatosis), a New Member of the Rheumatic Disorders. Ztschr. f. Laryng. Rhin. Otol., 35: 210, 1956.
6. Woodburn, C. C., Harris, H. E.: Idiopathic Lethal Granulomatous Ulceration of the Nose and Face. Clev. Clin. Quart., 18: 165, 1951.
7. Lindsay, S., Aggeler, P. M., Lucia, S. P.: Chronic Granuloma Association with Periateritis Nodosa; Report of a Case with Renal Failure. Am. J. Path,. 20: 1057, 1944.
8. Tuhy, J. E., Maurice, G. L., Niles, N. R.: Wegener's Granulomatosis. Am. J. Med., 25: 638, 1958.
9. Fienberg, R.: Necrotizing Granulomatosis and Angiitis of the Lungs. Am. J. Clin. Pathol., 23: 413, 1953.
10. Chomet, B., Pilz, C. G., Vosti, K., Levine, V.: Case of Wegener's Granulomatosis. Arch. Pathol., 66: 100, 1958.
11. Rose, G. A., Spencer, H.: Polyarteritis Nodosa. Quart. J. Med., 26: 43, 1957.
12. Sweeney, A. R., Baggenstoss, A. H.: Pulmonary Lesion of Periarteritis Nodosa. Proc. Staff Meet. Mayo Clin., 24-35, 1949.
13. Sandler, B. P., Matthews, J. H., Bornstein, S.: Pulmonary Cavitation due to Polyarteritis. Y.A.M.A., 144: 754, 1950.
14. Plumer, N. S., Angel, J. H., Shaw, D. B., Hinson, K. F. W.: Respiratory Granulomatosis with Polyarteritis Nodosa (Wegener's Syndrome). Thorax, 12: 57, 1957.
15. Fienberg, R., Necrotizing Granulomatosis and Angiitis of the Lungs and its Relationship to Chronic Pneumonitis of the Cholesterol Type. Am. J. Pathology, 29: 913, 1953.
16. Fahey, J. L., Leonard, E., Churg., J., Godman, G.: Wegener's Granulomatosis. Am. J. Med., 17: 168, 1954.
17. Weinberg, T.: Periarteritis Nodosa in Granuloma of Unknown Etiology; Report of Two Cases. Am. J. Clin. Path., 16: 784, 1946.
18. Walton, E. W., Leggat, P. O.: Wegener's Granulomatosis. J. Clin. Path., 9: 31, 1956.
19. Ahlstrom, C. G., Liedholm, K., Truedsson, E.: Respiratorenal Type of Polyarteritis Nodosa. Acta Med. Scand., 144: 323, 1953.

Surgery

Direct Surgery of the Abdominal Aorta and Its Distal Major Branches*

John Farr, F.R.C.S. (Edin.), F.R.C.S. (C)**

Direct surgery of the abdominal aorta and its distal major branches is being done with ever increasing frequency and constantly changing techniques. It is, therefore, appropriate to review from time to time the present surgical practice in this field and it is convenient to classify this subject by considering the situations that may lead to a direct surgical attack on any of these vessels.

Emergency Surgery

Trauma causing impaired blood flow.
Embolism causing impaired blood flow.
Aneurysm threatening rupture or leaking.

Elective Surgery

Arteriosclerosis causing occlusion.
Arteriosclerosis causing aneurysm.

Indications for Emergency Surgery

The emergency procedures that are sometimes necessary in patients suffering from trauma or embolism are relatively familiar because they have been fairly orthodox practice for many years. It must be stated, though, particularly in regard to embolism, that there are various and variable methods of management and it is proper to recall some pertinent clinical experience regarding both surgical trauma and embolism.

Trauma

When there is obvious impairment of circulation distal to an injury, exploration is obligatory. If this is carried out with reasonable care and skill, it is unlikely that anything but benefit can result. At the very least, a haematoma from a lacerated vein or artery may be evacuated and hemostasis secured. At the very best, it is entirely possible a limb or life may be saved. The details of surgery in such cases are so determined by the special situations found in each patient, that a description of local techniques is not practical; however, it is important to appreciate that loss of continuity of a major blood vessel due to trauma is no longer an indication for amputation, but rather an indication to restore arterial continuity.

Embolism

Embolectomy gives a very high proportion of satisfactory results if carried out within a reasonable time of the onset of the arterial obstruction.

It is my impression that this procedure is not done as frequently as it should be. In some cases the condition may not be recognized and this error can be corrected only by an increasing awareness of the possibility of this form of arterial obstruction. The well-documented fact that the conservative management of emboli yields a fair proportion of salvaged limbs no doubt influences surgeons to be less aggressive in dealing with these acute emergencies, and I think it is a more common reason for not performing embolectomy. The situation could be considered comparable to perforation of a peptic ulcer. While we know that conservative treatment will permit a certain number of patients to recover from peptic ulcer perforation, nevertheless, we also know that early and prompt surgical closure of such lesions is by far the best treatment from a point of view of morbidity, mortality and length of hospital stay. Similarly, when patients with acute arterial obstruction due to embolism, improve on conservative management, they do so because of their inherent capacity to establish a collateral circulation and not because surgery was omitted. If surgery is unsuccessful these patients will still establish their collateral circulation and if embolectomy is successful the patency of a major vessel will be restored. Patients in whom the embolus is **not** removed will still have an occlusion of a major vessel and the consequent diminished blood flow may result in sufficient impairment of function to cause significant symptoms.

It is not our practice to administer anticoagulants systemically to patients who have had an embolectomy. Heparin in weak dilutions is used in local irrigation at the time of surgery. If the embolus originated in the heart due to auricular fibrillation, the patient should be placed on permanent anticoagulants.

When auricular fibrillation is related to rheumatic heart disease, the assistance of a cardiologist should be sought to determine if a mitral commissurotomy is indicated. There is no doubt that this procedure has appreciably reduced the incidence of emboli in such patients.

Technical details of the procedure which are available in textbooks and other communications will not be given here. Arteriotomy is done at the site where the embolus is lodged, usually at the bifurcation of a vessel into two smaller branches. An exception to this is the saddle embolus of the aorta, in which a very satisfactory result can often be achieved by an indirect, bilateral and simultaneous approach through both femoral arteries.

Surgical removal of the embolus has a further advantage; frequently it is possible to extrude the very lengthy post-embolic soft clot that occurs in the vessel distal to the site where the embolus itself is lodged. Cannulization of the dorsalis pedis artery and the application of hydrostatic force to a cannula inserted in it, is a manoeuvre of some assistance in this regard.

*Based on a paper presented at the 50th Anniversary of the Manitoba Medical Association, October, 1958.

**Division of Surgery, Winnipeg Clinic, Winnipeg, Man.

Aneurysm

While it is convenient to classify the treatment of ruptured aneurysm under emergency surgery, it is more practical to consider details of such surgery while discussing the surgical treatment of aneurysms in general, and for this reason this third indication for emergency surgery will be considered in a later part of this paper.

Indications for Elective Surgery

Occlusion (Arteriosclerosis Obliterans)

The earliest symptom of impaired circulation in the lower extremity is usually intermittent claudication. Most frequently this is noticed in the calf, but it may be felt in the foot, the front of the leg, the thigh, the hip or the buttock. It should be appreciated that intermittent claudication may result from obstruction of the aorta or any of its branches going to the lower extremity. The fact that obstruction to the arterial flow may be proximal to the inguinal ligament may not be sufficiently recognized and it is proper to recall that Kekwick[4] who reviewed 53 consecutive cases of intermittent claudication, found objective evidence that the obstruction was proximal to the inguinal ligament in 11% of his cases. Regardless of the site of obstruction it is necessary to determine its extent and the status of the generalized arteriosclerosis by aortography or arteriogram as well as by a careful physical examination.

When treating patients suffering from intermittent claudication, it is important to remember that this is merely a peripheral manifestation of a generalized disease with a mortality much higher than the innocuous nature of the symptom would lead one to suspect. Hines and Barker sent questionnnaires to 280 Mayo Clinic patients who had intermittent claudication. Replies were received from 160 patients and of these 54.6% were dead within three years of reporting to the Clinic. The serious nature of the symptom, from both a local and a mortality point of view, is further emphasized by Spaulding's figures[5]; he followed 108 consecutive cases of intermittent claudication and found that the five-year mortality was approximately 25% and the amputation rate at the end of five years was also approximately 25%.

While these statistics are very sobering, it should be remembered that many of these patients can be greatly improved as far as claudication and amputation are concerned. Since there is no way of predicting which patients will die from the effects of their arteriosclerosis in other vital areas, we should treat the vascular obstruction in the limbs wherever it is troublesome and there is probability of success. If the obstruction is reasonably localized and if the vessel adjacent to the obstruction is reasonably free of atheromatous plaques, considerable and even dramatic improvement can be achieved by means of a bypassing operation (Fig. 1). It is acknowledged that the bypassing

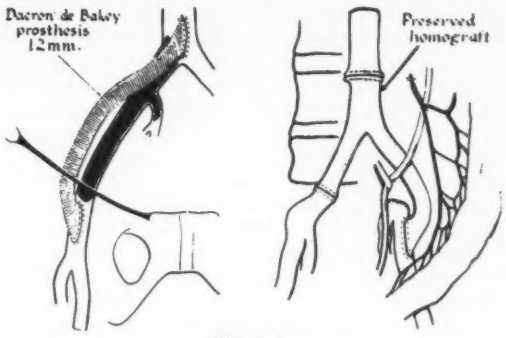


Figure 1

Two methods used in treating occlusive disease of the terminal aorta and iliac arteries.

procedure has several advantages over resection of the affected segment.

The details of technique relating to bypassing procedures are fully described elsewhere but it should be mentioned that variations in technique are especially noticeable in relation to the choice of material used in the bypass. It can be firmly stated, that the ideal and perfect prosthesis is not available at this time because either a textile prosthesis or a homologous graft, while accepted by the host, is still a foreign body. At the present time, it is generally acknowledged that teflon or dacron is the best textile for use in the aorta and iliac arteries. Various methods of weaving or knitting the textile are available and the choice of such a prosthesis is a matter of personal preference. It seems quite definite that homografts are no longer the prosthesis of choice for aortic replacements because an ever increasing number are being reported as showing aneurysmal dilatation after a variable length of time.

In vessels of the femoral and popliteal calibre homografts, textile prosthesis or autogenous vein grafts are equally acceptable. Although homografts seem to be technically easier to handle, obvious difficulties in procuring an adequate supply and occasional disasters resulting from inadequate sterilization have restricted their use in some centres. Whichever modality is used for bypassing the obstruction, it is realistic to anticipate a 25 to 30% failure at the end of two years. Nevertheless the graft is of great benefit to the remaining 70 to 75% of patients in whom it remains patent. If the bypass does occlude, the patient does not seem to be any worse than before the procedure.

Reference to thromboendarterectomy will be brief. This procedure was introduced with considerable enthusiasm, then temporarily it fell into disuse; however, at the present time Cannon is reemphasizing its value on this continent and I understand that in St. Mary's Hospital, London[1], it is the procedure of choice for occlusive disease of the iliacs and the aortic bifurcation. An overly

simplified description of the procedure is that it is an attempt to core out the occluded segment through an appropriate longitudinal incision in the artery and resuture the arteriotomy incision after taking appropriate measures to prevent vascular dissection of the vessel wall occurring at the distal end of the thromboendarterectomy.

Aneurysms

Aneurysms in general progress either to rupture or to thrombosis if the patient lives long enough.

Regardless of the patient's age, aneurysms in vessels distal to the aortic bifurcation should be treated surgically as soon as the diagnosis is made, otherwise the probability of losing the extremity is considerable. In view of the methods now available for restoring arterial continuity the operation can be confidently recommended and should be urged upon most patients. Even before the present techniques in grafting were perfected I resected aneurysms of the femoral artery without restoration of arterial continuity and without loss of the extremity.

Aneurysms of the major abdominal branches of the aorta occur, but, unfortunately, these usually present as an emergency or at autopsy. At the Winnipeg General Hospital in the last three months, there have been two cases of ruptured aneurysms of major visceral branches of the aorta, one of the celiac axis and the other of the renal artery. In such cases the diagnosis is usually limited preoperatively to severe internal hemorrhage, although in a ruptured aneurysm of the renal artery the retroperitoneal hematoma frequently may be felt in one or other of the lower quadrants.

The natural history of the untreated abdominal aortic aneurysm is difficult to state as each author has a different method of selecting his cases. For instance, Gliedman, Ayers and Vestal[3] reviewed autopsy protocols on all patients with abdominal aneurysm at King's County Hospital from 1940 to 1956. There were 68 such patients and of these 49% died of rupture of the aneurysm. On the other hand, Estes, who reviewed 102 patients with abdominal aneurysm found that 63% died of rupture and before the end of eight years all died (but not necessarily of rupture). One-third of his patients died before the end of the year following discovery of the aneurysm and two-thirds died within three and one half years. From these statistics and from clinical experience it is proper to regard an abdominal aortic aneurysm as a serious and potentially lethal condition and it is natural to compare the mortality of the untreated condition to the mortality of elective surgical treatment. As always, the mortality in elective surgical treatment is greatly conditioned by the selection of cases but an overall mortality of approximately 15.4% in a large series of consecutive cases which include some leaking aneurysms, has been reported.[2]

The diagnosis of abdominal aortic aneurysm can usually be established without difficulty by the presence of a mass which is expansile and pulsating. The absence of a bruit does not in any way exclude the diagnosis. On occasion a tumour mass overlaying the aorta or a pseudo pancreatic cyst, or a so-called "dynamic" aorta may cause some difficulty in diagnosis. A flat x-ray is often of value as it may reveal lines of calcification within the wall of the aneurysm or its laminated clot. Certainly it is not necessary to do an aortogram in most cases. In patients who have an aneurysm it has been observed that the blood pressure in the lower extremities is lower than, or equal to, the blood pressure in the arms. However, in many of these patients the popliteal pulse is absent because of co-existing arteriosclerosis and it is difficult to ascertain the blood pressure in the leg.

Some of the factors influencing the decision as to whether or not an operation should be performed in a patient with abdominal aortic aneurysm are:

Age—The patient's physiological age rather than his chronological age should be considered. This should not be a limiting factor however if there are signs of a leaking aneurysm.

Severe Arteriosclerosis — Manifestations of this condition elsewhere, particularly myocardial infarction, can be a contraindication, but, of course, if the aneurysm is leaking the outlook is so hopeless without interference, that resection should be done under such an emergency condition regardless of the contraindication. Recently I performed a successful operation on a patient of 75 years who had suffered a severe coronary infarction two years previously.

Size — It is important to consider the size of the aneurysm in reaching a decision. Although it is not possible to say that small aneurysms will not rupture, nevertheless Gliedman et al notice that in their necropsy material 72% of all aneurysms over 7 cm. were ruptured but only 18% of the aneurysms under 7 cm. were ruptured.

Symptoms—These are usually an indication for an operation. Pain frequently results from blood tracking through the laminated clot or expansion of the aneurysm.

The technique of resection of an abdominal aortic aneurysm (Fig. 2) is not too dissimilar from that

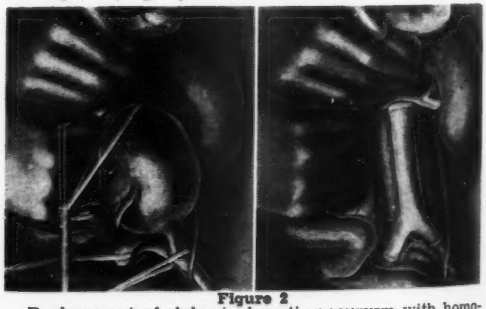


Figure 2

Replacement of abdominal aortic aneurysm with homologous graft. At the present time the use of textile prosthesis is to be preferred in this site because of occasional aneurysmal dilatation of the homologous graft.

used in obliterative disease of the bifurcation of the aorta except that the risk of rupture is always present. If the surgeon remembers to secure distal and proximal control of the vessels before proceeding with the dissection considerable technical difficulty can be avoided. Aneurysms of the abdominal aorta rarely thrombose, and, despite their thick layer of laminated clot, they rarely cause embolization in the distal vessels; however, embolization is not uncommon during the manipulation of surgical removal and this should be guarded against at the time of operation by distal clamping and heparinization of the distal vessels. It is generally stated that all arteriosclerotic abdominal aneurysms occur below the level of the renal arteries. This is sufficiently true to make aortography unnecessary in most cases, but, in some the aneurysm is so close to the renal arteries that resection is quite difficult. In such cases the Edwards-Tapp prosthesis with the funnelled proximal end is often of considerable assistance in restoring arterial continuity if it is sutured to the expanded aorta at the level of the renal arteries.

A manoeuvre of value is the application of bilateral pneumatic leg tourniquets which may be inflated just before the clamps are released at the completion of the anastomosis. This helps to prevent precipitous falls in blood pressure and the tourniquets may be reinflated several times after their deflation has shown the blood pressure to be not yet stabilized.

It should be remembered that the first successful resection and restoration of continuity of an abdominal aortic aneurysm was performed in 1951. Since then improved techniques and increased experience have resulted in a better prognosis for patients with abdominal aortic aneurysm. If the aneurysm is leaking or ruptured 100% mortality can be expected without surgical interference, but surgery can salvage a considerable number of these patients. If the aneurysm is uncomplicated, the judicious application of the newer surgical techniques offers the patient a real probability of restored health and active old age.

References

1. Downs, A.: St. Mary's Hospital, London, personal communication.
2. Ellis, F. Henry, Jr., Kirklin, John W., Bernatz, Philip E.: Surg. Clin. N. America, 37: 1047, Aug., 1957.
3. Gliedman, M. L., Ayers, W. B., Vestal, Betty L.: Ann. Surg., 146: 207, August, 1957.
4. Kekwick, A.: Quart. J. Med., XXI: 185, April, 1952.
5. Spaulding, W. B.: Canad. M.A.J., 75: 105, July 15, 1956.

Biochemistry

Some Recent Advances in Clinical Biochemistry

M. C. Blanchaer, B.A., M.D., C.M.

Department of Biochemistry, St. Boniface Hospital and the Department of Physiology and Medical Research, University of Manitoba

"Don't confuse change with progress."
—Anon.

Because of the size and the activity of this field, it is necessary to select for review only a few of many possible topics.

Increasing use is being made of test papers to detect urine glucose ("Testape," "Clinistix"), protein ("Albustix"), ketones ("Ketostix") and both glucose and protein ("Uristix"). The specificity of "Testape" and "Clinistix" for glucose suggests that for the rapid screening of urines, these enzyme test papers are superior to nonspecific tablets and powders such as "Clinitest" and "Galatest" based on copper or bismuth reduction. The latter, however, offer the advantage of detecting lactose, galactose, pentose and homogentisic acid, which are missed by the enzyme papers. The advantages of using both types of tests was brought to our attention recently by a strongly positive "Clinitest" and a negative "Clinistix" test in the urine of a patient with alkaptonuria. He had been told he was a diabetic, presumably because of the strong false positive copper reduction produced by the homogentisic acid in his urine which, in fact, was free of glucose.

"Albustix" and "Uristix" are quite sensitive to protein but false positives occur occasionally in highly coloured urines. The manufacturers state that both the glucose and protein test papers give quantitative results. However, for maximum reliability, it is better to use such tests for qualitative screening only and to analyze positive specimens by standard quantitative methods.

The "Acetest" tablet, commonly used to test for acetoacetate and betahydroxybutyrate in urine, can also be used[1] to detect plasma ketone bodies over the critical level 50 mgm.% when applied to plasma diluted with one volume water. The simplicity of this test recommends its use in suspected diabetic coma, particularly when urine ketones are absent, as may occur with dehydration sufficient to produce oliguria.

There have appeared recently a number of commercial kits to determine a variety of other substances in serum. One that deserves wider use, particularly in smaller laboratories, is "Fibrindex," a rapid qualitative test for plasma fibrinogen which has proved invaluable for the detection of afibrinogenemia in post-partum hemorrhage. On the other hand, kits for measuring serum lactic dehydrogenase, alkaline phosphatase and the two transaminases, although sound in principle, can produce quite erroneous results in the hands of technicians unaware of the sensitivity of these enzymes to inhibitors that abound in the average laboratory.

Of the recently introduced serum enzymes, the serum glutamic oxalacetic transaminase (SGOT) has been used and abused most widely: The clinical applications of this enzyme and the biochemical basis of the test have been summarized in a readily understood presentation[2]. A more extensive non-critical review[3] is also available.

It is now generally accepted that the SGOT almost never is normal 24 hours after a myocardial infarct. Thus, an elevated SGOT may be used to differentiate infarction from conditions producing similar signs and symptoms in which the SGOT is usually normal, such as myocardial ischemia and pulmonary embolism. However, the routine ordering of the SGOT in the average case of suspected infarct is unwarranted since it very rarely gives information unobtainable by conventional methods. Indeed, the sensitivity of the SGOT to minor degrees of hepatic impairment can lead to a false diagnosis of myocardial infarction in the presence of congestive failure[4]. It is also important to realize that anticoagulants such as bishdroxycoumarin ("Dicumarol") will themselves elevate the transaminase when administered after myocardial infarction[5]. This phenomenon is thought to be a direct effect of the anticoagulant on the liver parenchyma which appears to be more susceptible to these drugs after myocardial infarction.

The SGOT is elevated in a variety of hepatic disorders, including infectious hepatitis, infectious mononucleosis, cirrhosis and malignant metastatic invasion of the liver[6]. Although obviously non-specific, a raised SGOT is a useful indication of hepatic cell necrosis. Thus, the SGOT level in infectious hepatitis is very high in the pre-icteric stage and may be the deciding diagnostic point in atypical cases[7]. In chronic hepatitis and cirrhosis, the changing levels of SGOT usually reflect the activity of the disease, remaining elevated during periods of hepatic parenchymal destruction and falling towards normal during remission. In view of this correlation, it is interesting that the SGOT will often show changes independent of those in the serum bilirubin, the flocculation tests and the bromsulphalein retention. This independence is particularly well shown in the effect of alcohol on the SGOT of chronic alcoholics[8]. The SGOT elevation in biliary disease is not striking, but levels in acute cholecystitis and cholangitis may be somewhat higher than those in biliary obstruction when infection is not marked[9]. This test has not proved very useful in differentiating between the jaundice of obstruction and that caused by hepatic parenchymal damage, except perhaps in the newborn[10]. Earlier hopes that the cerebrospinal fluid level of GOT might differ in various types of neurological disorders have not been fulfilled[11]. The high concentration of GOT and other enzymes in skeletal muscle has been applied to detecting the Duchenne type of muscular dystrophy[12, 13]. In this condition, the release of GOT, aldolase, lactic dehydrogenase and other enzymes from the muscle into the plasma occurs very early in the disease, often before signs of muscular impairment become marked. Thus, in this disease, as in infectious hepatitis, the early elevation of the SGOT can be a key diagnostic point.

In order to determine how much liver disease might contribute to raised SGOT levels in complex diagnostic problems, the originators of the SGOT test introduced another serum transaminase, the SGPT[14]. The SGPT (serum glutamic pyruvate transaminase) is very high in acute hepatitis, but relatively normal levels are said to occur in cirrhosis and after myocardial infarction. Thus, an elevated SGOT in the presence of a normal SGPT might be expected to eliminate the liver as a source of these enzymes. Unfortunately, it has been our experience[15] that the SGPT is often sufficiently elevated after an infarct to raise some question as to whether the simultaneous rise in the SGOT has its origin from the damaged myocardium or from a congested liver. This decision is further complicated by the rise in both SGOT and SGPT produced by anticoagulants[5]. It would seem wise, therefore, to refrain from placing too much reliance on the SGPT:SGOT ratio until the specificity claimed for it is confirmed by workers other than the originators of the test.

The increasing number of serum enzyme estimations being done on patients with acute abdominal pain has revealed a surprising incidence of elevated amylase and lipase levels in cases which do not present with the classical signs and symptoms of acute pancreatitis. Some of these patients seem to have a mild pancreatitis, but in many the increase in lipase and amylase appears to be secondary to inflammation in the region of the pancreas. Recently, new evidence has been published[16] supporting the older view that the milder, atypical attacks of pancreatitis are less likely to be missed if the urine amylase is determined instead of the serum amylase. It has been claimed[17] that serum trypsin estimations will detect pancreatitis and pancreatic carcinoma. Confirmation of the value of this test has as yet not been reported.

Of the dozen or so new serum enzyme tests other than the transaminases that have been proposed as diagnostic tools, only the serum lactic dehydrogenase (SLD) has been assessed reasonably adequately. First suggested[18, 19] as a test for cancer, SLD was soon found[20, 21] to be elevated in myocardial infarction, in certain types of leukemia and in the megaloblastic anemias. The increased SLD originally reported to be present in 95% of patients with cancer was subsequently found to occur only after extensive metastatic spread to the liver. The increase in the SLD after myocardial infarction was confirmed[22] and shown to be absent in coronary insufficiency and myocardial ischemia. In contrast to the marked rise in SGOT produced by kidney

and liver disease, the SLD is only moderately affected by those conditions, permitting its use for the detection of myocardial infarction in the presence of liver and kidney disease. The superiority of the SLD over the SGOT as an aid in the detection of myocardial infarction was confirmed by White[23], who found the increase in SLD after infarction to persist longer than the rise in the SGOT. The usefulness of SLD determinations in various neoplastic conditions has also been investigated[24, 25]. In myelocytic leukemia and in certain lymphomas, the changes in the SLD give an objective indication of the activity of the disease, falling during remission and rising during relapse. Attempts are also being made to use the LD levels of spinal and ascitic fluids to detect diseases of the structures bathed by these fluids. The preliminary results[26] appear promising, but are as yet unconfirmed.

The fad for serum protein electrophoretic analysis seems on the wane. No doubt the realistic assessment of this time consuming test has been delayed by the aesthetic appeal of the electrophoretic strips. However, it is now generally agreed that there are, in fact, few instances when serum protein electrophoresis gives significant new information. These exceptions include the proof of agammaglobulinemia and perhaps the detection of an abnormal globulin in multiple myeloma. However, the more subtle variations in the serum alpha-1, alpha-2, beta- and gamma-globulins have little diagnostic specificity[27].

Most electrolyte analyses nowadays have a standard of reliability exceeding that warranted by the use to which the results are put. However, there remains in common use the CO_2 combining power, a test that was introduced in 1917 by Van Slyke[28], who, three years later[29], discarded it as inadequate and replaced it with a measurement of the plasma CO_2 content. It is an interesting comment on medical progress that 37 years later, CO_2 combining power is still requested some twenty times more frequently than the plasma CO_2 content, in spite of the fact that the CO_2 combining power underestimates the severity of the bicarbonate disturbance in all varieties of acidosis and alkalosis[30].

The current interest in lipid metabolism in relation to atheroma has brought to the fore the difficulties encountered in cholesterol determination. The clinical significance of these analytical problems has recently been discussed in a paper[31] that should be read by those who prescribe low-fat diets on the basis of single serum cholesterol estimation.

There is increasing evidence[32] that radioactive protein-bound iodine (PBI) estimations can replace the more difficult PBI test in many instances. The radioactive PBI also appears to be a more reliable method of detection of hyperthyroidism than the I^{131} uptake by the thyroid.

The tubeless ("Diagnex Blue") method of detecting gastric anacidity has come into general use as a screening procedure, although it is not reliable in the presence of kidney disease[33, 34]. With this reservation, the "Diagnex Blue" procedure can be considered an ideal innovation, in that it relieves the patient of discomfort, simplifies the laboratory's work and no doubt pleases the manufacturer, since the materials cost at least ten times those needed for a conventional gastric analysis. Unfortunately, this test offers little comfort to those of us who believe that it and the fractional gastric analysis were made obsolete long ago by superior methods of detecting pernicious anemia, ulcer and gastric carcinoma.

References

1. Nabarro, J. D. N.: Biochemical Investigations in Diagnosis and Treatment, 2nd ed. Little, Brown and Co., Boston, 1958.
2. LaDue and F. Wroblewski: Modern Medicine of Canada, 2: 101, 1956.
3. Conrad, F. G.: New England J. Medicine, 256: 602, 1957.
4. DuToit, C. H.: Proc. New England Cardiovascular Society, 1955-56, XIV, p. 36.
5. Wroblewski, F. and C. Manso: J.A.M.A., 167: 2163, 1958.
6. Wroblewski, F. and J. S. LaDue: Annals of Int. Med., 43: 345, 1955.
7. Wroblewski, F. and J. S. LaDue: J.A.M.A., 160: 1130, 1956.
8. Bang, N. V., Iversen, K., Jagt, T. and S. Madsen: J.A.M.A., 168: 156, 1958.
9. Madsen, S., Bang, N. V. and K. Iverson: Brit. Med. J., 1: 543, 1958.
10. Kane, S., Goldstein, S. and F. Wroblewski: J.A.M.A., 168: 860, 1958.
11. Myerson, R. M., Hurwitz and T. Sall: New England J. Med., 257: 273, 1957.
12. Pearson, C. M.: New England J. Med., 256: 1069, 1957.
13. Soltan, H. and M. C. Blanchaer: J. Pediatrics (in press).
14. Wroblewski, F. and J. S. Ladue: Annals of Internal Medicine, 45: 801, 1956.
15. Bebchuk, W. and M. Blanchaer: Unpublished results.
16. Saxon, E. J., Hinkley, W. C., Vogel, W. C. and L. Zieve: Arch. Int. Med., 99: 607, 1957.
17. Nardi, G. L. and C. W. Lees: New England J. Med., 258: 797, 1958.
18. Hill, B. R. and C. Levi: Cancer Research, 15: 514, 1954.
19. Hill, J. H.: J. Nat. Cancer Institute, 18: 307, 1957.
20. Wroblewski, F. and J. S. LaDue: Proc. Soc. Exper. Biol. Med., 90: 210, 1955.
21. Zimmerman, H. J. and H. G. Weinstein: J. Lab. Clin. Med., 48: 607, 1956.
22. Wacker, W. E. C., Ulmer, D. D. and B. L. Vallee: New England J. Med., 255: 449, 1956.
23. White, L. P.: New England J. Med., 255: 984, 1956.
24. Bierman, H. R., Hill, B. R., Reinhardt, L. and E. Emory: Cancer Research, 17: 660, 1957.
25. Blanchaer, M. C., Green, P. T., Maclean, J. P. and M. J. Hollenberg: Blood, 8: 245, 1958.
26. Wroblewski, F., Decker, B. and R. Wroblewski: New England J. Med., 258: 635, 1958.
27. Sunderman, F. W. and F. W. Sunderman, Jr.: Am. J. Clin. Path., 27: 125, 1957.
28. Van Slyke, D. D.: J. Biol. Chem., 30: 347, 1917.
29. Stadie, W. C. and D. D. Van Syke: J. Biol. Chem, 41: 191, 1920.
30. Jacobi, H. P., A. J. Barak and M. Beber: Clin. Chem., 3: 631, 1957.
31. Rivin, A. V., Yoshino, J., Shickman, M. and O. A. Schjeide: J.A.M.A., 166: 2108, 1958.
32. Silver, S.: Advances in Clinical Chemistry, 1: 111, 1956.
33. Radman, T., Gutman, A. and R. M. Myerson: J.A.M.A., 167: 172, 1958.
34. Rosenthal, H. L. and S. Buscaglia: J.A.M.A., 168: 409, 1958.

Dermatology

Progress in Dermatology, 1958

Saul S. Berger, M.D.

The major advance in Dermatology was an announcement by Dr. Harvey Blank of the University of Miami on the use of Griseofulvin, an oral antibiotic for treatment of fungous infections of the skin. Griseofulvin is a metabolic product of Penicillium griseo fulvum dierckx. Dr. Blank made this announcement in December 1958 at the American Academy of Dermatology and Syphilology. While Dr. Blank had only thirty-eight cases in which the new medication was tried, the new drug was eminently successful, and promises to be a major break through in the treatment of heretofore resistant fungous infections of the skin and nails, particularly of the superficial variety.

The Lancet of December 6, 1958 reports on the Oral Treatment of Ringworm with Griseofulvin. This article reports nine cases with clinical Trichophyton rubrum infections of the skin or nails under treatment with this drug with excellent results. T. rubrum infections of nails and skin have hitherto resisted all forms of therapy. One case of Microsporon Aedouini has been treated with good results. The M. Aedouini infections are serious ring worm infections of the scalp, often necessitating X-ray epilation for cures.

Dr. Harvey Blank gave the drug orally in dosages of 1 - 2 grams a day. The drug is undergoing extensive clinical trials before it is decided to make it available for general medical use. The drug apparently produces a colchicine like effect on cells stopping multiplication of cells. In the cases of tinea corporis there was improvement in one to two weeks. While not all superficial fungous infections of the skin in the small series of reported cases have been helped, the most hitherto resistant cases and the most frequently seen have shown remarkable response to therapy with Griseofulvin. Those helped by Griseofulvin are Trichophyton Rubrum, Microsporon Versicolor, Microsporon Canis, Trichophyton Capitis (Aedouini), Trichophyton Pedis (Mentagrophytes and Rubrum), and Onychomycoses due to Trichophyton Rubrum.

The drug has not proven effective for monilial infections or the deep mycoses. So far no serious side effects have been reported with this drug. As the article in the Lancet points out it may be many months before the use and limitations of the drug can be well established and cases followed up for a sufficient length of time.

Dermatology in 1958 has no major therapeutic advances to report. Planing or Dermabrasion for Acne Scars is now a well established procedure. Improvement in Acne Scars runs from about forty to sixty percent. The diamond fraize for planing has come into use and is much easier to use and safer than the wire brush.

The new oral Steroids such as (1) triamcinolone (Aristocort and Kenacort); (2) dexamethasone (Deronil and Decadron), (3) one 6 methyl-delta-1-hydrocortisone (Medrol) have not enlarged the scope of Dermatologic Therapy. Topically triamcinolone acetonide has proven to be a valuable addition to the dermatologic armamentarium.

There have been no advances in the therapy for Psoriasis. Alphosyl Lotion is no more effective than solutions of Coal Tar in most cases. Except in severe and generalized exfoliative dermatitis following psoriasis, steroids are contraindicated for psoriasis. Psoriasis is often more refractory after steroid therapy.

The use of newer and safer, and longer acting Sulfonamides have proven useful to control the pustular acne cases. Tetracyclines are still used for the pustular acne cases. These drugs have to be used over a considerable period of time, but can be employed in dosages of 250 milligrams a day or every other day as a maintenance dose.

The use of ten percent Sodium Chloride in an ointment base has proven helpful in cases of icthyosis. Dr. Franz Hermann of New York University Post Graduate Medical School regards an increase in the transepidermal water supply of the stratum corneum and a consequent increase in the hydration of its base as responsible for the beneficial action.

The use of Penicillinase for the chronic penicillin reactions has proven effective. One injection of 800,000 units given intramuscularly will keep the blood clear of penicillin for four to five days.

Temaril (Smith, Kline and French) has some use as an anti pruritic agent especially in Atopic Dermatitis. The drug has an anti histamine, sedative, tranquilizer and hypnotic effect.

The use of Cantharidin Powder 0.7 percent in equal parts of acetone and Flexible Collodion has proven effective in some cases of Periungual warts, but like all treatments for warts it has a great number of failures.

Hylenta CD*

penicillin G potassium

No. 888 — "Hylenta" CD* Tablets (500,000 I.U.)
No. 890 — "Hylenta" Mitis CD* (250,000 I.U.)

- Both granule coating and tablet base are resistant to gastric acid.
- Both disintegrate rapidly in the alkaline medium of the upper small intestine.
- The released penicillin produces a high blood level within the hour.
- This level is maintained longer than those provided by unprotected other penicillin tablets.

also available

No. 891 — "Hylenta" Forte AR** (1,000,000 I.U.)

No. 903 — "Hylenta" Liquid (250,000 I.U. per tsp.)

and where a sulfonamide is also desired

No. 904 — "Hylenta"-S Liquid (250,000 I.U. + 0.5 Gm. sulfamethazine per tsp.)

No. 887 — "Hylenta"-S CD* Tablets (250,000 I.U. + 0.5 Gm. sulfamethazine).

***Controlled Disintegration base**

****Acid-Resistant coating**

Ayerst

Ayerst, McKenna & Harrison Limited, Montreal

They all like "PREMARIN"

- The menopausal patient . . . because "Premarin" imparts a noticeable feeling of well-being, as well as relieving the distressing symptoms.
- The husband . . . because the patient on "Premarin" therapy can well be described as "easier to live with". Improvement in mental outlook is often dramatic.
- The doctor . . . because "Premarin" is so remarkably effective in relieving menopausal symptoms. "Premarin" doesn't just mask symptoms – it replaces what the patient lacks – natural estrogen.

"Premarin"— a complete natural estrogen complex — is available as tablets of various potencies, and also in combination with meprobamate or methyltestosterone.

Ayerst

Ayerst, McKenna & Harrison Limited, Montreal

COLLEGE OF GENERAL PRACTICE

Manitoba Chapter

THIRD ANNUAL SCIENTIFIC AND BUSINESS MEETING

Auditorium, Medical College, Emily at Bannatyne

Monday and Tuesday, June 1st and 2nd, 1959

Monday, June 1st
Auditorium, Medical College

Morning

8.00 Registration.

9.00 Tranquilizers,
Mark Nickerson, M.D.

9.30 E.N.T. Problems in General Practice,
M. M. Pierce, M.D.

10.00 Exhibits and Coffee Break.

11.00 Common Disorders and Mistakes in Gastric Diagnosis,
J. H. Geddes, M.D., London.

12.00 Lunch in College Cafeteria.

Afternoon

1.00 Collagen Diseases,
Wm. Fyles, M.D.

1.30 Carpal Tunnel Syndrome,
F. R. Tucker, M.D.

2.00 Exhibits and Coffee Break.

3.00 Obscure Abdomen,
Panel.

6.30 Annual Dinner Meeting of College Members,
Medical Arts Club Rooms.

☆

Registration Fee $10.00
14 Hours Credits

Tuesday, June 2nd
Auditorium, Medical College

Morning

8.00 Registration.

9.00 Newer Virus Entities,
J. C. Wilt, M.D.

9.30 Leucorrhea,
Cam McInnes, M.D.

10.00 Exhibits and Coffee Break.

11.00 Some Peculiarities of Surgery in Children,
S. Kling, M.D., Edmonton.

12.00 Lunch in College Cafeteria.

Afternoon

1.00 Volvulus,
George Waugh, M.D.

1.30 Small Bowel Insufficiency,
J. H. Geddes, M.D., London.

2.00 Exhibits and Coffee Break.

3.00 Tinea Capitis in Manitoba,
Arthur R. Birt, M.D.

3.30 Renal Biopsy and Disease,
Ashley Thomson, M.D.

6.30 Annual Dinner and Dance,
Highwayman.

☆

Special Ladies' Program

'hydropres'

(HYDROCHLOROTHIAZIDE WITH RESERPINE)

The direct approach to all degrees of hypertension

Mild • Moderate • Severe

With increased effectiveness
to establish better control in
more hypertensives at a fraction
of previous dosage requirements

'hydropres'

- *May arrest the organic changes of hypertension*
- *Greatly reduces or entirely eliminates anginal pain*
- *Appreciably lessens the need for dietary salt restriction*
- *Usually promptly relieves anxiety, headache, dizziness, palpitations and tachycardia*
- *Practically eliminates fluid retention*
- *Simplifies the dosage regimen*

supplied:

'Hydropres'-50 and 'Hydropres'-25.
Each tablet contains 50 or 25 mg. 'HYDRODIURIL'
(hydrochlorothiazide) with 0.125 mg.
reserpine. In bottles of 100 and 1000.

A product of Merck Sharp & Dohme research

'Hydropres' and 'HYDRODIURIL' are trade-marks of Merck & Co. Limited

MSD

Merck Sharp & Dohme
Division of Merck & Co. Limited
Montreal 30, Que.

Editorial

S. Vaisrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

The Common and the Rare

No textbook description of a disease or a syndrome is complete without a reference to its incidence. This "incidental" intelligence is, obviously, given for purposes other than mere satisfaction of idle, albeit legitimate curiosity. It is meant to aid the epidemiologist and public health specialist in planning his campaign of prophylaxis, the hospital administrator in his allocation of services, the drug manufacturer in his estimation of supply and demand. Above all, it is intended to help the clinician by facilitating his diagnostic approach through proper statistical orientation.

Armed with correct statistical data, the physician is better prepared to exercise the subtle art of balancing diagnostic probabilities. Equipped with precise knowledge of what is common and what is rare, he is less apt to look for canaries, and more likely to favor sparrows in diagnostic deliberations. Given proper perspective, he is prone to perceive the prevalent, which is thrown into bold relief, and is ready to relegate the rare to the background, where it belongs.

This is all to the good. There is, however, another side to the coin. Statistical orientation often leads to myopic concentration on the common and amblyopic neglect of the rare. It tends to make the physician lose interest in the latter and dismiss it from his mind. This is regrettable, for the rare has an important role to play in medicine, a role which transcends its statistical insignificance.

Perhaps, it may be worthwhile at this point to give a passing thought to the alleged statistical insignificance of rare diseases. It may be worth remembering that some of the rarities of yesterday are common today, and it may well come to pass that many current curiosities will become commonplace tomorrow. Polyarteritis nodosa and disseminated lupus erythematosus were but a few years ago exotic entities. Their incidence in many areas today is higher than that of rheumatic fever. Multiple myeloma was until recently one of the canaries of medicine. Today, although not quite a sparrow, it is by no means a rare bird. Hashimoto's disease, the erstwhile struttting peacock of the medical ward rounds, is fast losing its glamor as many new cases come to the fore. Pheochromocytoma, aldosteronism, argentaffinoma, Wegener's disease, rare as they are today, may cease to be so in the future. Whether this loss of rareness be due to increasing frequency or greater awareness, it is significant in that it detracts from the significance of statistical insignificance.

So much for statistics. Let us be reminded, however, that the "common" and the "rare" are not used exclusively as synonyms for the frequent and the infrequent. Sometimes they express value judgments. The common may be equated with the ordinary and vulgar, the trite and commonplace ("above the vulgar flight of common souls"), the rare with the fine and distinguished, the precious and sublime, ("And what is so rare as a day in June"). It may well be that in medicine too the rare may partake of this quality of distinction which is undimmed by statistical scarcity.

The detection of a rare disease is a thrilling experience for the medical sleuth. It inflates his ego, bolsters his pride and enriches his conversational repertoire. It elicits a sense of elation akin to that experienced by a philatelist who discovers a valuable stamp in an otherwise undistinguished collection, or an art collector who stumbles upon a rare masterpiece in an old second hand shop. Conversely, it is a most frustrating experience for the clinician faced with a rare disease to miss the diagnostic boat, as he sees it sail for the shores of Pathology.

It is not to be inferred, however, that the importance of a rare disease lies solely in the gratification of a collector's whim or an artist's fancy. Like all works of art its value extends beyond the purely aesthetic end. The dazzling rare "creation" worn by the lovely at the ball is aimed not so much to impress by its beauty, as to attract attention to its wearer and to stimulate the desire for exploration. So has a rare disease a similar effect, for it too draws attention to fundamentals and invites investigation.

Basic research and discovery owe a great debt to the study of rare diseases. Where, indeed, would be our understanding of the process of coagulation, without the challenge of hemophilia, Christmas disease and afibrinogenemia? Where would our recent concepts of bilirubin metabolism be without the stimulus of Gilbert's disease and Dubin-Johnson syndrome? Would our knowledge of inborn errors of metabolism be as advanced as it is today without the spur of phenylketonuria, aminaciduria, galactosemia, porphyria, Van Gierke's disease? Would our awareness of the actions of serotonin be there at all without the study of carcinoid tumors?

These questions are largely rhetorical, demanding no answers. It can be confidently stated that none of the advances referred to above along with the many unmentioned would have been possible, without the prompting of rare diseases which challenged the inquisitive mind.

The Manitoba Medical Review is proud to publish in this issue a review of the relatively uncommon syndromes of hyperadrenocorticism by E. Perry McCullagh and a report of an extremely rare case of Wegener's granuloma by M. Van Wijhe. It welcomes these excursions into the uncommon. Canaries interspersed among sparrows brighten the literary landscape for the discerning reader blessed with rare judgment and common sense.

Ed.

Abstracts from the Literature

Treatment of Rheumatoid Arthritis with Chloroquine: H. Fuld and L. Horwich. B.M.J., p. 1199, November, 1958.

The literature on the use of chloroquine in the management of rheumatoid arthritis is reviewed. Results in treatment and following up 39 patients from three months to four years are described.

Complete remission of the disease process was obtained in 30% of cases, a major improvement occurred in 50%, and insignificant or no benefit was noted in about 20% of the patients.

The drug proved harmless and was well tolerated in larger doses than used by other authors. Relapses whilst on chloroquine were not observed in this series.

The authors recommend a regime of treatment consisting of bed rest, induced pyrexia, blood transfusions, and salicylates during the first three weeks of treatment, and tablets of chloroquine sulphate, 200 mg. t.d.s., throughout the treatment or immediately after induced fever — this dose of chloroquine to be continued until a remission has been obtained, when the dose may be decreased to 400 mg. daily (equals 300 mg. base). The maintenance therapy may be required for 12 months or longer. The authors have given up corticosteroids for systemic treatment of rheumatoid arthritis altogether.

A. Rogers.

☆

Etiologic Factors in Obstruction of the Superior Vena Cava: A Pathologic Study. Failor, H. J., Edwards, J. E. and Hodgson, C. H. Proc. Staff Meet. Mayo Clin., 33: 671 (Dec. 10), 1958.

Superior vena caval obstruction due to various mediastinal diseases is an infrequent condition as judged by the small number of reported cases. Slight degrees of compression may cause no symptoms and few clinical signs, while complete obstruction may occur without the development of either significant symptoms and signs in rare instances. Collateral pathways include the internal mammary, vertebral, azygos and lateral thoracic veins, depending in part on the level of the obstruction.

The authors studied 33 cases of superior vena caval obstruction that came to necropsy. In 28 cases, the obstruction was due to malignancy, mainly bronchogenic carcinomas and lymphomas. A benign teratoma caused obstruction in one case, and chronic mediastinitis was the etiological factor in the remaining four instances. In several cases, signs of caval obstruction were not noted prior to death. Roentgen therapy had been attempted in 11 patients without apparent alleviation of the obstruction. In all cases secondary to bronchogenic carcinoma, there was invasion and penetration of the wall of the superior vena cava. When the obstruction is due to a benign lesion, the initial symptoms of the patient were usually related to the obstruction, when the obstruction was secondary to malignancy, other symptoms usually predominated.

G. A. Lillington.

☆

Pyroglobulinemia: Further Observations and Review of 20 Cases. Martin, W. J., Mathieson, D. R. and Eigler, J. O. C. Proc. Staff Meet. Mayo Clin., 34: 95 (Feb. 18), 1959.

Dysproteinemia is a term applied to those states characterized by abnormalities of the blood proteins. There may be congenital or acquired deficiencies of normal protein fractions (agammaglobulinemia), or the presence of blood proteins that are abnormal in quality or quantity (paraproteinemia). The paraproteinemias include macroglobulinemia, cryoglobulinemia and pyroglobulinemia. In the latter condition, the serum contains heat-coagulable substances which are detected inadvertently during the performance of serological tests for syphilis. In ten of the 20 cases discovered in this manner, multiple myeloma was present, but no constant relationship seemed to occur between the presence of heat-coagulable serum globulins and hyperproteinemia, albuminuria or Bence Jones proteinuria. Of the remaining 10 patients, three had no underlying disease demonstrable, and one patient each had lymphosarcoma, carcinoma of the esophagus, lupus erythmatosus, macroglobulinemia, convulsive disorder, hypervitaminosis D, and a systemic illness of undetermined nature. Macroglobulinemia developed ten years later in the patient with hypervitaminosis D. Only four patients had a normal sedimentation rate, and only six had a normal hemoglobin concentration. Like the other two paraproteinemias, pyroglobulinemia may be idiopathic or associated with diseases such as multiple myeloma, cancer and collagen diseases; unlike cryoglobulinemia and

macroglobulinemia, there does not appear to be a hemorrhagic diathesis associated with pyroglobulinemia.

G. A. Lillington.

☆

The Hepatic Hilar Lymphatics of Man: H. Baggenstoss and J. C. Cain. New Eng. Journal of Medicine, Vol. 256, March 21, 1957, p. 531.

The mean number of lymphatics draining the liver in the hepatoduodenal ligament is greater in cases in which ascites is present and in cases in which cirrhosis is present, with or without ascites, than in routine autopsy cases in which ascites is absent. In cases of cirrhosis the lymphatics not only are dilated but also have thickened walls.

The factors probably of importance in producing the increased size and number of lymphatics are venous stasis, intrahepatic portal hypertension and tissue destruction and inflammation. The thickening of the lymphatic walls in cirrhosis may be an indication that lymph has been flowing under increased pressure for a long time. The possibility that inflammation is also a factor in causing the thickening is considered.

A. Rogers.

Book Review

The Practise of Sanitation: Hopkins & Schultz. Third edition, published by the Williams & Wilkins Company of Baltimore, 1958, $8.00.

It is seldom that one finds a well balanced and up to date description of what constitutes a sanitary environment and how this state can be achieved in the light of modern knowledge.

Such is the case with this handsomely-bound volume containing over 140 well chosen illustrations. The text covers in moderate detail every phase of sanitary control as practised by health authorities.

In describing these practises the authors make use of allied material to be found in the subjects of bacteriology and parasitology.

Among the many new additions to a sanitary text are such items as milking parlors, the matter of fluoridation, and the pollution of water supplies by radio-active isotopes. A section on Industrial Hygiene is well written and stimulates one to wider reading in this field.

This book should be read by every medical student and should be used by all graduates proceeding towards their Diploma in Public Health.

J. S.

Association Page

Reported by M. T. Macfarland, M.D.

Report of the Professional Policy Committee

February 1959.

This report will contain the recommendations of the Professional Policy Committee regarding the revision of the M.M.A. Fee Schedule.

During July 1957, following a joint meeting with representatives of the M.M.S. Executive, the M.M.A. Officers and the Professional Policy Committee (P.P.C.) the need for a relative value Fee Schedule was agreed upon.

Following the decision of the Canadian Medical Association at its Edmonton Convention that year (1957) to set up an Economics Department, the P.P.C. was advised January 23, 1958 to "discontinue a relative value fee study, but to continue receiving changes in the fee schedules determined by the specialty groups in order that our own schedule may be revised."

As a consequence, early in 1958 the P.P.C. set about obtaining fee schedules from various specialty sections and blocs. As has already been reported to you (Annual Report 1958) it was September before submissions from all groups became available.

Rather than request a simple listing of items and suggested fees, the committee asked each group to incorporate with each suggested fee item the current M.M.S. and W.C.B. allowance, plus the fee from the new schedules recently published by the Alberta and Saskatchewan Divisions. In retrospect it can be said that the Committee appreciated fully the heavy task the assembling of this data meant to several Sections and blocs. When edited and tabulated, however, the P.P.C. had a comprehensive and current appreciation of the fee situation.

It is safe to say that without this extra detail the whole process of fee revision would have been seriously handicapped. Our sincere appreciation of the co-operation that met our numerous requests is hereby recorded. Special credit too should be reserved for Dr. D. Parkinson who undertook to carry out the basic editing and tabulating of the various submissions.

At this juncture, it should be recorded that all our early consideration of fee data raised the question of whether or not we were to produce a fee schedule which incorporated a fee differential between generalists and specialists. Here was a tremendously important basic policy which, unless decided upon at the outset, would enter and complicate all our subsequent deliberations. Although our decisions have already been reported to the Executive Committee, it is important to reaffirm that the proposals we are putting forward at this time represent a continuation of the single schedule which was used in the "Minimum fee schedule for Medical Practice," the M.M.A. book which we were asked to review.

Earliest consideration of the new fee submissions indicated that a very widespread upward revision of fees was being requested. From its inception, the P.P.C., taking in part its cue from the Report of the Special Commission, had been greatly impressed by the "Relative Value Study" developed by the California Medical Association. When the unit values in this study were set down against the material outlined above, it became apparent that there existed very close, in fact amazingly close correspondence with the values given in the data supplied by our own groups.

Again it is important to relate that casual review of the California plan incites respect for its thoroughness, curiosity regarding the items in which an individual reviewer is interested and skepticism regarding its general validity, particularly in a community 2,000 miles away and in another country. The perspective of our committee was, however, quite different in that, week by week, as situations were tried against the California plan, time and again equitable answers were obtained.

At this stage, committee members undertook to review with those they represented, the bloc or section reaction to the possible implementation of the California formula. The reaction to this procedure was encouraging in that several of the larger groups agreed to go along with the California formula so long as the rest did likewise. It would not be fair to state that bloc reactions were always enthusiastic or entirely favorable. All have agreed to go along with the California plan as a means of getting a mature unit index established.

As a consequence, the following motion was recently passed. **That the professional policy committee recommend the adoption of the listing and unit values contained in the second edition of the California Medical Association plan.** Two minor items were excepted and a massive revision of the inadequate listing of items under Pathological examinations was agreed upon.

It is interesting to note that, at the same time that the above decision was being made, the House of Delegates of the American Medical Association meeting in Minneapolis in December had this to say—quoted from Journal December 20, 1958—2148.

"In a related action, the House decided to face the very important problem of relative value studies. Relative value studies are not fee schedules; rather, they are attempts to show (by unit or point

DARICON

oxyphencyclimine

ANTICHOLINERGIC
ANTISECRETORY
ANTISPASMODIC

SUPPLY: Each white scored tablet contains 10 mg. of oxyphencyclimine hydrochloride. Bottles of 100.

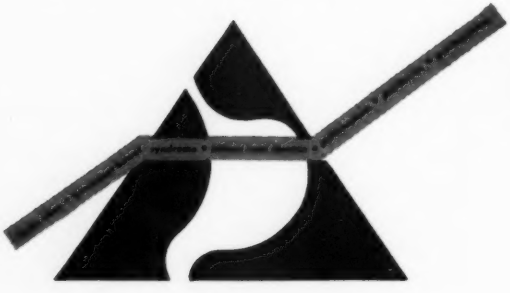
DARITRAX

OXYPHENCYCLIMINE WITH ATARAX

ANTICHOLINERGIC
ANTISECRETORY
ANTISPASMODIC
TRANQUILIZER

SUPPLY: Each pink scored tablet contains: 10 mg.-oxyphencyclimine, 25 mg.-hydroxyzine hydrochloride (Atarax). Bottles of 100.

EVEN REFRACTORY CASES RESPOND



One tablet b.i.d. gives
full time relief

Pfizer *Science For The World's Well-Being*

PFIZER CANADA
(Division of Pfizer Corp.)
5330 Royalmount Avenue,
Montreal 9, P.Q.

12259

designations) the relationship between time, competence, effort and experience, and other factors required to perform a professional service as compared with those required for other professional services. In accepting a committee on Medical Practices report calling for relative value studies, the House of Delegates agreed that:

Unless Medicine does undertake this activity, it may be done by others who are less qualified. The House of Delegates approves in principle the conducting of Relative Value Studies by each constituent Medical Association rather than a Nationwide study or Regional Studies. The nomenclature descriptions and code numbers of the California Relative Value Study (almost identical with those of Kansas and Iowa) can well be accepted as a national format."

Insofar as the indexing and coding are concerned it would appear that, pending the development of the promised C.M.A. material, the California study is sound.

Unlike most of its predecessors, the California plan breaks new ground when it covers Medical Services. In the old M.M.A. Schedule all Consultations were covered by one item. In the California plan under the heading Special Medical procedures, nine items are listed proceeding from "Office visit necessitating professional care over and above routine office visits" for which 1.5 units are allowed, up to "Consultation requiring complete examination" for which seven units are given. In an address to the Western Conference of Prepaid Medical Care Plans at Portland, Oregon, November 1957, Francis Cox, M.D., one of the chief architects of the California plan, emphasized the very great importance of recognizing formally the great variety of responsibilities carried under "Special Medical procedures" which have tended heretofore to be omitted from schedules or consolidated into one or two entries. At the same time he recognized the danger such listings represented if they were to be abused and emphasized the heading "Special" and the introductory narration which outlines that written reports should be furnished on request to validate the performance of the described services which involve more care than can be provided in the ordinary office, home or hospital visit.

Subsequent to the above decision to recommend the adoption of the California plan the Committee by separate motion recommended that **the initial unit value for all sections be three dollars and fifty cents in relation to the cost of living index as of January 1, 1959.**

Because this plan pioneered in this area and represented primarily an effort to develop a unit index rather than a dollar fee index, each of the sections — Medical, Surgical, Radiological, etc. was set up separately — each bearing the warning that the relative values of one section should not be related to the relative value in another. Many precedents exist, however, for the setting of one unit value for all sections. The Iowa "Unit Fee Index" referred to in the A.M.A. reference above is dated January 11, 1959. It carries the same format as the California plan uses and a $5. per unit valuation in all sections, and unit values that are only **occasionally** revised upwards or downwards from the California plan. In asking consideration of this recommendation, the Committee requests careful Executive Committee consideration of the narrative portions of page 13 dealing with Medical Services (Items 011 and 012 have been deleted) and of page 17 dealing with Surgery and Anaesthesia. These pages have been considered in detail by the Professional Policy Committee and are recommended in toto for incorporation in a Manitoba Unit index. At the same time the consideration of a "preamble" to the proposed fee schedule is requested. This preamble represents an attempted synopsis of some of the matters discussed in this report and an outline of some of the principles involved in the use of a "Unit fee index."

H. M. Malcolmson, M.D.,
Chairman.

Preamble

The special commission of the M.M.A. (1956) recommended that a "Relative Value Fee Schedule" be studied as the basic fee schedule of the M.M.A. During 1957 the Professional Policy Committee was instructed to commence work upon such a fee schedule for Manitoba.

After studying fee schedules submitted by every block of practice in Manitoba and comparing these with the schedules of other Provinces and with the "Relative Value Study" of the California Medical Association, the Committee recommended the adoption of the "California Plan."

The advantages of the "California Plan' include the following:

(1) It represents an internationally recognized schedule, expressed in units and offers a uniform nomenclature and index that would be of great value in statistical study and fee negotiation.
(2) It provides a means whereby medical fees may be correlated with alterations in the cost of living index by periodic adjustments in the dollar value of each unit.
(3) It permits the submission of accounts in units to any group underwriting medical services.
(4) It offers a means whereby interblock fee correlation may be simplified.

The four sections included in the California Plan have been preserved and an extra section on anaesthesiology has been added. They outline and establish a relative value expressed in units for:

A. Medical Services
B. Surgical procedures
C. Radiological procedures

D. Laboratory and Pathological procedures
E. Anaesthesiology.

By making this breakdown the dollar value of a section's unit may be altered from time to time according to experience and equity without disturbing the whole schedule.

This fee schedule is intended for use as a guide. Higher fees may be charged in cases presenting complications or requiring unusual skill, responsibility and time, in cases where immediate attention is demanded during office hours or where the patient insists upon extra or unwarranted attention. Fees may, of course, be reduced if the schedule fee would produce a financial hardship.

Relative Value Fee Schedule

The Professional Policy Committee has recently reported to the Executive of the Manitoba Medical Association regarding a Relative Value Fee Schedule for Manitoba. This report is published elsewhere in the Review. The following paragraphs are written in explanation of how this was developed and what it means.

The original Relative Value study was started by the California Medical Association in 1953 and completed in 1956. A revised, or second edition was adopted by the California Medical Association Council in November, 1957. It is this 48-page revised edition that is referred to in the report of the Professional Policy Committee.

At the outset, four general principles were deemed to be essential. First, a suitable and uniform nomenclature was needed to describe various procedures and services. Secondly, a standardized code system to meet the needs of actuaries, statisticians, and others dealing with fee schedules was considered vital. Thirdly, the system creates a relative value schedule but expresses itself in units rather than in dollars. Finally, it was considered essential to break the schedule into four separate segments dealing with: a) Medical procedures, b) Surgical, c) Radiological and d) Laboratory and Pathological procedures. To this the P.P.C. has added a fifth for Anaesthesiology, although this is included with surgery in the California plan. It is emphasized in the California plan that the unit values set out in each section are based on the relative value for procedures for that section only, and ought not to be related to the values expressed for procedures of any other section.

The foreword contained in the revised edition of the California Medical Association plan details some of the reasons for the use of units rather than dollars. These are quoted verbatim as follows:

1. The standards for relative values for fees were established by survey of the membership of the California Medical Association. The level of fees varies throughout the state under the influence of many factors but analysis of the survey results reveals that the relationship between fees for most procedures remains almost the same, even in widely separated geographical areas. Expressed in dollars these relationships would have been misleading and incorrect for many areas. Expressed in units, they are accurate and useful.

2. Health insurance in California today requires fee schedules and indemnity schedules at many different dollar levels. California Physicians Service needs different fee schedules for different income ceiling plans. Many groups want to buy indemnity insurance that pays benefits approximating the usual fees charged by physicians. Others want adequate protection at a low premium and will accept an element of co-insurance. The relative value study expressed in units, may be used as a guide in setting any and all of these schedules with widely varying dollar levels but retaining a constant relationship between fees.

3. The relative value study will require changes to keep abreast of the changes in medicine; as procedures are introduced, others become obsolete. New methods of doing the same procedure increase or decrease the amount of time or skill required, with a resulting change in the compensation the physician should receive for the service. Changing a fee schedule expressed in dollars is difficult and often requires years of work and negotiation. The relative value study expressed in units can readily be changed by the results of new surveys from time to time which are recommended by the Committee on Fees. Thus, the standards can be changed to reflect new facts of medical practice. Changes in the dollar schedules can follow one by one.

It will readily be seen that the above reasoning is applicable universally and not only in California.

It is also to be pointed out that the system of using unit values does not set anyone's fees or fee schedule. It merely relates the value set upon various procedures and is intended for use as a guide only. The dollar value per unit can be varied from one locality to another or from one year to another depending on the general level of prosperity. As an example the dollar value per unit which might be suitable in the wealthy centers of Ontario might be far out of line with that permissible in Newfoundland. Or the dollar value per unit might be tied to the cost of living index as suggested in the P.P.C. report so that doctors are not the last to move up the inflationary spiral.

In their deliberations, the Professional Policy Committee was early beset by the problem of the differential fee schedule used by the Manitoba Health Services. In its conclusions, the P.P.C. did not set up a dual schedule. Having studied the proposed fees from various procedures as submitted by the various sections of the Manitoba Medical Association and having found them in reasonably close accord with the California schedule, it recommended only the single relative value schedule of that Association. The P.P.C. has therefore recommended this schedule as a replacement for the Minimum Fee Schedule for Medical Practice of the

Manitoba Medical Association. Further, as a minimum fee schedule, it was recommended that the unit value be set at $3.50 per unit.

To translate units into dollar values, one simply multiplies the number of units for a given procedure by the dollar value per unit. Thus using the $3.50 figure, the first office visit of a new patient, being rated at 2.0 units, works out to $7.00. An appendectomy rated at 35.0 units works out to $122.50. A hemoglobin estimation rated at 0.3 units becomes $1.05. There is no need at this time to go further into the values for specific services or procedures. However, the reasons for stating that the values assigned under the five sections of the plan should not be compared one section with another might be considered.

For example, if the cost of operating a laboratory increased so the presently stated unit value failed to cover expenses, an increase in this unit value would be in order. If it applied to all sections equally, the value of a total gastrectomy would also be raised, unnecessarily, and if the increase were from $3.50 to $4.00 per unit, a complete blood count would then be $4.00, but the total gastrectomy would go from $350. to $400. It might equally be necessary to increase the value of office consultations, and if so, all items on the section in medicine would increase but this would not automatically raise the fees for radiology.

The report of the P.P.C. has been under active consideration by the M.M.A. Executive at its meetings of 15th March and 5th April. At the March meeting the listings and unit values contained in the second edition of the California Plan were adopted. In the end, the $3.50 value per unit was rejected and, at the time of this writing, no dollar value has been set per unit.

R. H. McFarlane,
Liaison Editor.

☆

Central District Medical Society

A meeting of the Central District Medical Society was held at Portage la Prairie on Wednesday, March 11th, 1959.

Present were Doctors: T. W. D. Miller, Oakville, President; R. E. Renaud, Portage la Prairie, Secretary-Treasurer; Drs. G. M. Black, G. H. Hamlin, G. Lowther, D. Rae, J. C. Rennie, E. Snell, C. M. Thomas, Portage la Prairie; E. R. Ford, MacGregor; Ed Johnson, Selkirk; Hugh S. Provis, Treherne; J. G. Smith, Gladstone; and J. D. Adamson, B. D. Best, J. M. Bowman, E. G. Brownell, J. H. Dirks, M. T. Macfarland, and H. D. McIntosh of Winnipeg.

The afternoon session was held in the Dining Room of the Portage General Hospital. The speakers were: 1. Dr. Brian Best, Winnipeg, "Kielands Forceps," 2. Dr. Ted Brownell, Winnipeg. "Rheumatic Heart Disease," 3. Dr. Jack Bowman, Winnipeg, "Respiratory Emergencies."

At the business session held in the afternoon the following officers were elected for the year 1959-60:

President, Dr. Glen Lowther
Vice-President, Dr. J. G. Smith of Gladstone
Secretary-Treasurer, Dr. C. M. Thomas
Representative to Executive Committee of Manitoba Medical Association, Dr. C. M. Thomas.

Due to the length of program few accepted the kind invitation for the conducted tour of the Hospital.

Following refreshments and dinner at the Portage Hotel, greetings from the Manitoba Medical Association were extended by the President, Dr. Ed Johnson of Selkirk. A presentation by Dr. J. D. Adamson, consultant to the Manitoba Hospital Service Plan evoked spirited discussion. Dr. M. T. Macfarland, Executive Director, discussed various aspects of the Association work in the field of current legislation.

The hope was expressed that meetings of the District Society will be held at more frequent intervals.

M. T. M.

☆

North of 53 Medical Society

A meeting of the North of 53 District Medical Society was held at Flin Flon, April 2nd and 3rd, 1959.

Those attending included: Drs. Percy Johnson, A. Marrack, P. Premachuk, N. Stephansson, H. K. Stinson and G. N. Willson of Flin Flon, Dr. J. M. McMahon of Lynn Lake, Dr. Edward Johnson, Selkirk, Drs. Joseph Leicester and R. Seifer of The Pas, Drs. J. D. Adamson, F. W. DuVal, J. M. Lederman, M. T. Macfarland and J. T. McDougall of Winnipeg.

Detained in Winnipeg by fog the plane carrying several visitors arrived late, but through the courtesy of Mr. E. W. Austin, General Manager of the Hudson Bay Mining and Smelting Company Limited a tour of the plant was carried out as arranged.

A reception and buffet dinner was provided by Dr. and Mrs. Norman Stephansson following which members attended a scientific session in the Clinic Board Room. The first speaker was Dr. J. M. Lederman, Associate Professor of Pathology and Secretary of the Faculty of Medicine, University of Manitoba, whose subject was "Pathology of Peripheral Vascular Disease." The second speaker was Dr. J. T. MacDougall, Lecturer in Surgery, University of Manitoba, whose subject was "Peripheral Vascular Disease."

Following the scientific program members were entertained at the home of Dr. and Mrs. G. N. Willson. The group listened with great interest to the radio broadcast of the hockey semi-finals game which the Flin Flon Bombers won from Edmonton.

The Business and Scientific Session was resumed on Friday morning with election of the following officers for the year 1959-60:

President:
Dr. J. M. McMahon, Lynn Lake.
Secretary-Treasurer:
Dr. H. K. Stinson, Flin Flon.
Representative to the Manitoba Medical Association Executive:
Dr. A. L. Jacobs, The Pas.

Dr. Fred W. DuVal, Winnipeg, a former resident at Flin Flon, spoke on the subject of "Skin Grafting."

Dr. J. D. Adamson, Winnipeg, Medical Consultant to the Manitoba Hospital Services Plan, discussed problems related to the operation of the Plan.

Greetings were extended by the President of the Manitoba Medical Association, Dr. Edward Johnson, Superintendent of the Mental Diseases Hospital at Selkirk. Dr. Johnson also visited two brothers who reside in Flin Flon.

Dr. M. T. Macfarland, Winnipeg, Executive Director, outlined some of the activities of the Association and complimented the Society on the local representatives, Dr. H. L. McNicol, Flin Flon, who is Second Vice-President, and Dr. A. L. Jacobs, The Pas. Recipient this year of the Winnipeg Clinic Foundation Bursary Award to a general practitioner was Dr. J. Leicester, The Pas.

Following the meeting a luncheon was arranged at the General Hospital through the courtesy of Reverend Sister Dion and other staff members. The nurses' dining room was decorated for the occasion. A vote of thanks was made by Dr. Percy Johnson.

The Winnipeg party left Flin Flon on the afternoon plane.

M. T. M.

☆

Obituary

Dr. William Ewart Campbell

Dr. William Ewart Campbell, prominent ophthalmologist, died on April 7th after a long illness. Born in Minnedosa, 1885, he was educated in Winnipeg schools, Manitoba College and Manitoba Medical College from which he graduated in 1912. From 1915 to 1919 he served with the R.C.A.M.C., then took postgraduate work in Glasgow Royal Infirmary, Edinburgh and London. He practised in Winnipeg with the late Dr. S. W. Prowse and from 1931 till 1947 he was on the teaching staff of the Faculty of Medicine. From 1939 to 1947 he was head of the department of ophthalmology. He was president of the Winnipeg Medical Society and the Manitoba Medical Association (1939-1940). He retired from teaching in 1947 but continued practice till 1957. He is survived by his wife, four sons, one of whom, Dr. J. S. Campbell, practices at Fort William, and nine grandchildren.

Social News

Reported by K. Borthwick-Leslie, M.D.

So, I'm late with my column and holding up the publication. Sorry, but please pin the blame on the subtle homicidal tactics of the Press interpreting, or possibly misinterpreting statements from the "Profession." Quote: **"City Doctors Fighting Tough Asia Flu Virus."**

If you have the following symptoms, call your doctor **immediately:** "Headache, fever, general aches and pains throughout the body, of course there is no known medical treatment and no antibiotic to control the virus, but get cracking and phone your doctor immediately anyway." — Nuts. That's where the homicide comes in — who gets phoned? The internist and poor already overworked and underpaid General Practitioners. Who is being killed by the "A" bug — seven patients **and** the doctors. Now, after the damage is done, the public has a sporting 1,000 to 1 odds as to who will konk first — patient or doctor.

So that's why our publication is being held up. Anyone any idea how many people in Winnipeg have headaches? Gardening, golfing pains and aches? Druggists report on unprecedented sale of thermometers, no one knows how to read 'em, but that's O.K.

I had one 3 a.m. call — barely audible "Come quickly, my husband has a temperature of 104°." So away we go — on **my** thermometer 99.4 and the comment, "But doctor, that's not the way to take it." By the good old Sherlock Holmes methods I finally found that to keep things nice and clean she washes the hands in hot water, carefully inserts the thermometer holding the mercury tip in her hot little moist hands — at 3.45 — 10 miles from Fort Garry. Homicide?

Phooey to blabbermouths.

☆

Had a phone call from Doris Gowron last week. The General Practitioners' Women's Club of Manitoba — a flourishing "going" group — are most anxious to get, and keep in touch with **all** ladies associated with our Manitoba Group of General Practitioners.

It is an impossible task to trace all individual members, new graduates, new arrivals, etc., so **please,** all wives, potential wives and interested parties, call Mrs. Tony Gowron, VE 2-3645, or Mrs. Glenn Hamilton, ED 1-6123. There are numerous important and interesting functions looming on the horizon — you will not be sorry you registered.

Charles M. Burns, M.D., F.R.C.S. (C), announces the new location of his office at 221 Medical Arts. Practice limited to Consultant Surgery. All best wishes, Charles.

☆

Congratulations to Dr. Roy Stewart, the first M.D. to become Illustrious Potentate of Khartum Temple, A.A.O.N.M.S., Oasis of Winnipeg.

Indeed an honor for Dr. Stewart, and a mighty big responsibility.

☆

There has been an exodus of our members to scientific meetings, conventions in all geographical points, but cannot name 'em all, so just hope they all have fun and learn a lot.

☆

Welcome to Our Babies

Dr. and Mrs. Harry Lander proudly announce the arrival of Debra Ann (isn't that a cute name), on April 5, 1959. Baby sister for Samuel Mark and Terry Lynn.

☆

Dr. and Mrs. A. A. (Sandy) Campbell are very happy about the arrival of Lawrence Kenneth, April 17, 1959, brother for Peter, Craig and Alison. One more girl, Sandy, and you have a full house.

☆

Dr. and Mrs. Cornelius Derksen proudly welcome Carol Anne, April 16, 1959.

☆

Dr. and Mrs. E. C. Shaw welcomed, March 9, 1959, Margaret Alison, baby sister for Janet and Sandra.

☆

Dr. and Mrs. Waldo M. Yule announce the birth of their son, Geoffrey Waldo, on April 13th, in Exeter, England. Dr. Yule is doing post-graduate work at the Princess Elizabeth Orthopedic Hospital in Exeter, remaining another year. Thank you, Dr. Yule, Sr.

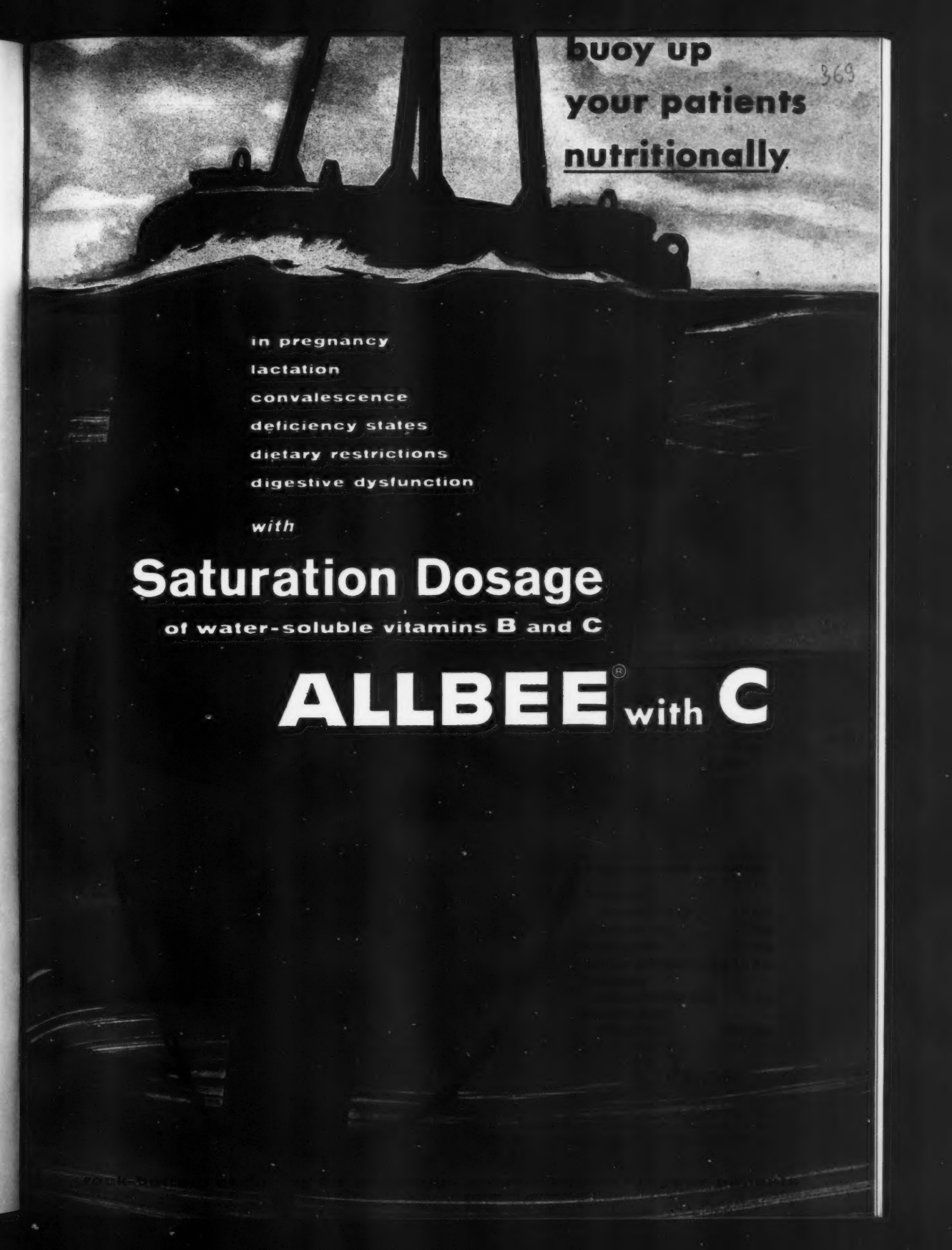
☆

Good night, am now putting my own aching muscles to bed — fatigue, not "A" virus.

HOSPITAL MEETINGS

Hospital	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Children's	12:00 Surgical Rounds	10:00 Staff Rounds "B" Service 12:00 Postgraduate Seminars	9:30 Staff Rounds "C" Service 11:00 Clinical Path. Conference 11:00 Death Review (4th Wednesday)	11:00 Grand Ward Rounds	10:00 Staff Rounds "A" Service 12:30 Clinical Luncheon (1st Friday)	9:00 Newborn Conference
Deer Lodge	Clinical Luncheon (1st Monday)			11:00 Ward Rounds		
Grace		Clinical Luncheon (3rd Tuesday)	9:00 Paediatrics 9:45 Medicine 10:30 Ob. & Gyn. 11:15 Surgery	12:00 - 2:00 p.m. Weekly Seminar		
Misericordia	Tissue Committee (3rd Monday)	Clinical Luncheon (2nd Tuesday)				8:30-12:30 Ward Rounds
Municipal			7:30 p.m. Review of Deaths (2nd Wednesday)			8:30 Clinical Staff Conf. and Ward Rounds
St. Boniface	9:00 Paediatric Rounds	11:00 Surgical Rounds	9:00 Obstetrical 11:00 Grand Rounds 12:30 Cardiac Unit (4th Wednesday)	11:00 Tumor Clinic 12:00 Clinical Luncheon (2nd & 4th Thurs. ex. July & Aug.)		
St. Boniface Sanatorium	12:30 Clinical Luncheon (1st or 2nd Monday)					
Victoria					Clinical Luncheon (3rd Friday)	
Winnipeg General		11-12:00 Medical Ward Rounds	9-10:00 Tumor Clinic 10-11:00 Surgical	12:15 Clin. Lunch. (1st & 3rd Thurs.)		
Brandon General			Medical Staff Lunch (Wed. prior to 2nd Tues. each month)			10:00-noon Clinical Drs. from S.W. Manitoba invited (Nov. to May)

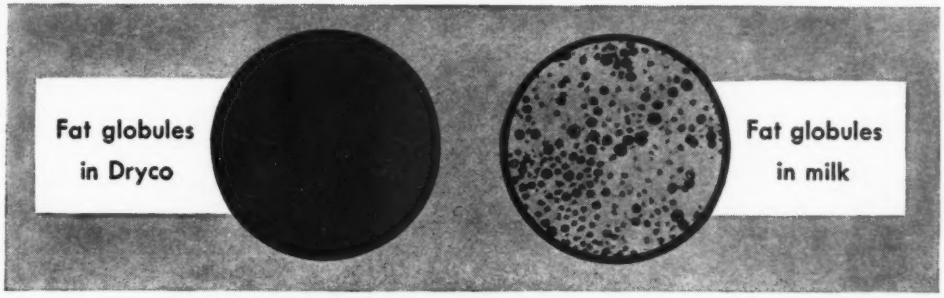
367

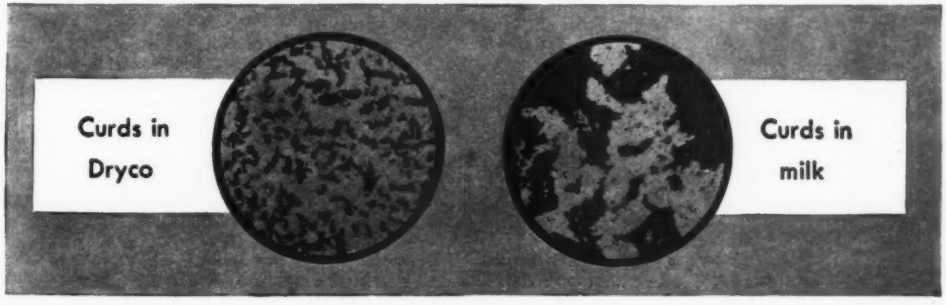

buoy up
your patients
nutritionally
in pregnancy
lactation
convalescence
deficiency states
dietary restrictions
digestive dysfunction
with
Saturation Dosage
of water-soluble vitamins B and C
ALLBEE® with C

DRYCO–ideal formula for normal infants as well as prematures

343

1. **High Protein-Low Fat Ratio:** 2.7 to 1 ratio of protein to fat facilitates preparation of *low-fat* formulas which assure *ample protein intake*—to meet the normal growth requirements of early months in normal infants *and* the tissue-building diet requirements of premature and malnourished infants.
2. **Carbohydrate Flexibility:** Dryco's moderate lactose content permits flexible regulation of carbohydrates at the doctor's discretion. Dryco may be used: alone; with added carbohydrate; with added whole milk; or with added carbohydrate and whole milk.
3. **Extreme Digestibility:** Fat globules and protein curds in Dryco are more digestible.





DRYCO

For further information write: **THE BORDEN COMPANY LIMITED,**
Formula Foods Department, Spadina Crescent, Toronto.

for all those patients who do better on hormones

Schering hormones are minutely standardized, uniformly controlled and biologically adjusted to assure the results you desire at a cost your patients appreciate.

Combined estrogen-androgen—additive relief for menopausal women.

gynetone repetabs
(Ethinyl Estradiol with Methyltestosterone)

gynetone injection
(Estradiol Benzoate with Testosterone Propionate)

Specific androgen therapy—for the elderly and in the male climacteric.

oreton
(Testosterone)
Oral, Injection, Pellets

Estrogens—for the female climacteric.

estinyl tablets
(Ethinyl Estradiol)

Progestins—in habitual abortion, dysmenorrhea and menstrual disorders.

pranone tablets
(Ethisterone)

proluton
(Progesterone)
Injection, Buccal Tablets

ON YOUR PRESCRIPTION ONLY

Schering
CORPORATION LIMITED MONTREAL

SCHERING HORMONES *in modern practice.*

Detailmen's Directory

Representing Review Advertisers in this issue, whose names are not listed under a business address.

Abbott Laboratories
G. J. Bowen ..... GR 5-4559
R. G. (Bud) Harman ..... LE 3-7509
Alan (Al) M. Grant ..... AL 6-0125
Bruce Hunter ..... GL 2-5263

Ayerst McKenna and Harrison
W. R. Card ..... HU 9-7115
C. C. Savage ..... SU 3-4558
Jack Ostrow ..... ED 4-3240
Wm. J. O'Grady ..... WH 2-8211

Bencard, C. L.
W. J. Tarbet ..... HU 9-4438

Borden Company Ltd.
Ken Hodges ..... AL 3-4319

British Drug Houses
W. S. Langdon ..... GL 3-1325
H. Harvey ..... TU 8-5341
G. G. Rieder ..... HU 9-5803

Ciba Company Ltd.
Edward Stephany ..... HU 9-7292
Leslie D. MacLean ..... CE 3-3240

Connaught Laboratories
Brathwaites Ltd. ..... WH 2-2635

Frosst, Charles E.
W. M. Lougheed ..... HU 9-3963
W. J. McGurran ..... AL 3-0722
E. R. Mitchell ..... HU 9-6164
R. P. Roberts ..... AL 3-4032

Hoffmann-La Roche Limited
Paul E. Prendergast ..... AL 3-1962
Wilf Baldwin ..... HU 9-8236

Lederle Laboratories
J. G. Jonasson ..... SP 5-4862
W. C. Hall ..... HU 9-2207
J. E. Smith ..... AL 3-0437

Merck, Sharp and Dohme (Canada) Ltd.
W. G. Ball ..... GR 5-5702
Noel J. Pritchard ..... GL 2-6880
E. J. Strimbicki ..... AL 3-5767

McNeil Laboratories of Canada Ltd.
B. M. Coutts ..... JU 2-5920

Nadeau Laboratory Ltd.
Andrew Desender ..... CH 7-4909

Ortho Pharmaceutical Corp.
Don MacDonald ..... GL 3-4549

Parke Davis & Co.
L. W. Curry ..... HU 9-1138
B. S. Fleury ..... GL 3-7071
R. J. Robinson (Brandon) 92-288
J. B. Peters ..... VE 2-3862

Pfizer Canada
E. E. Conway ..... TU 8-1193
W. R. Mitchell ..... GL 3-6226
W. G. Johnston ..... TU 8-1391
Blake Johns ..... SP 5-1404

Riker Pharmaceutical Co. Ltd.
John R. Falconer ..... GL 3-5385

Robins (Canada) Ltd., A. H.
Harold Tetlock ..... SP 5-5624
Fred Gallinger ..... ED 4-1367

Sandoz Pharmaceuticals Ltd.
H. D. Robins ..... ED 8-8216

Schering Corp. Ltd.
Halsey Park ..... HU 9-4346
John D. Nicolson ..... LE 3-4447
Allan L. Segal ..... HU 9-7701

Schmid (Canada) Ltd., Julius
H. V. Walker ..... LE 3-8664

Searle & Co., G. D.
Harry Chambers ..... LE 3-6558

Smith, Kline & French Inter-American Corp.
Boyd C. Affleck ..... VE 2-1237
Bob Court ..... ED 8-8093

Squibb & Sons, E. R.
A. B. Shaen ..... GL 2-9859
M. G. Waddell ..... GR 5-1552

Warner-Chilcott Labs.
A. L. (Andy) Argue ..... TU 8-1619
Gordon Harrower ..... AL 3-4147

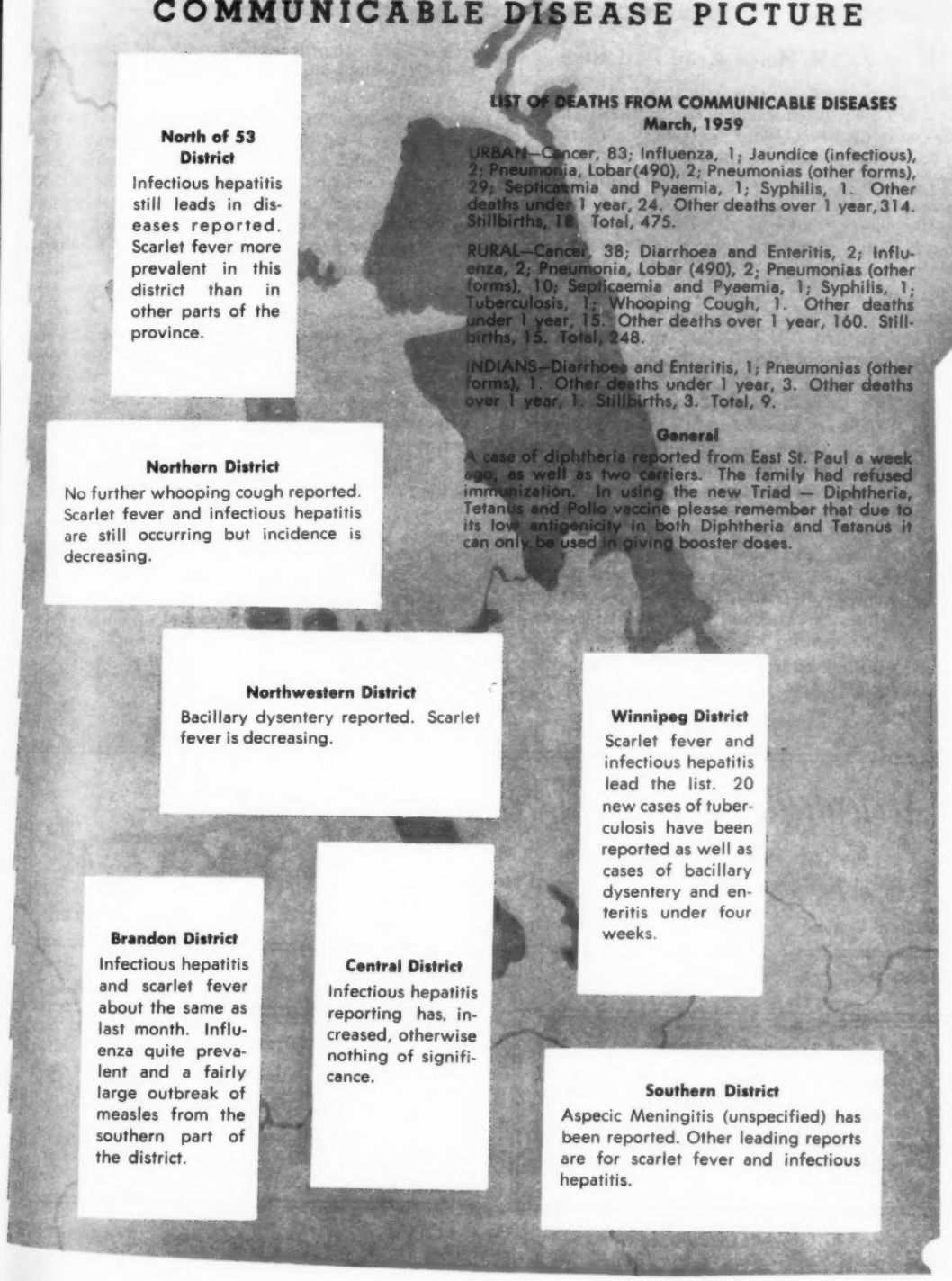
Will, Charles R.
A. C. Payne ..... VE 2-2055

Winthrop Laboratories
R. M. Kelly ..... Res. GR 5-6038
A. E. Pauwels ..... CE 3-2024

Wyeth & Brother, John
A. W. Cumming ..... HU 9-5694
Stuart Holmes ..... JU 9-4273

DEPARTMENT OF HEALTH & PUBLIC WELFARE

COMMUNICABLE DISEASE PICTURE



North of 53 District

Infectious hepatitis still leads in diseases reported. Scarlet fever more prevalent in this district than in other parts of the province.

Northern District

No further whooping cough reported. Scarlet fever and infectious hepatitis are still occurring but incidence is decreasing.

Northwestern District

Bacillary dysentery reported. Scarlet fever is decreasing.

Brandon District

Infectious hepatitis and scarlet fever about the same as last month. Influenza quite prevalent and a fairly large outbreak of measles from the southern part of the district.

Central District

Infectious hepatitis reporting has increased, otherwise nothing of significance.

Winnipeg District

Scarlet fever and infectious hepatitis lead the list. 20 new cases of tuberculosis have been reported as well as cases of bacillary dysentery and enteritis under four weeks.

Southern District

Aspecic Meningitis (unspecified) has been reported. Other leading reports are for scarlet fever and infectious hepatitis.

LIST OF DEATHS FROM COMMUNICABLE DISEASES
March, 1959

URBAN—Cancer, 83; Influenza, 1; Jaundice (infectious), 2; Pneumonia, Lobar(490), 2; Pneumonias (other forms), 29; Septicaemia and Pyaemia, 1; Syphilis, 1. Other deaths under 1 year, 24. Other deaths over 1 year, 314. Stillbirths, 18. Total, 475.

RURAL—Cancer, 38; Diarrhoea and Enteritis, 2; Influenza, 2; Pneumonia, Lobar (490), 2; Pneumonias (other forms), 10; Septicaemia and Pyaemia, 1; Syphilis, 1; Tuberculosis, 1; Whooping Cough, 1. Other deaths under 1 year, 15. Other deaths over 1 year, 160. Stillbirths, 15. Total, 248.

INDIANS—Diarrhoea and Enteritis, 1; Pneumonias (other forms), 1. Other deaths under 1 year, 3. Other deaths over 1 year, 1. Stillbirths, 3. Total, 9.

General

A case of diphtheria reported from East St. Paul a week ago, as well as two carriers. The family had refused immunization. In using the new Triad — Diphtheria, Tetanus and Polio vaccine please remember that due to its low antigenicity in both Diphtheria and Tetanus it can only be used in giving booster doses.

Victorian Order of Nurses

How V.O.N. Helps Aged Patients

Care of the aged — especially those ill or helpless — is a growing problem in Canada. Here is an actual case history of how home nursing care by the V.O.N. helps solve this problem.

She was in her eighties and had been discharged from hospital following an operation for a broken hip. She was bedridden, confused, completely helpless and with no family except her husband to look after her.

Knowing all this, her doctor nevertheless felt she would be better off at home. He arranged for the Victorian Order of Nurses to care for her. A hospital bed was obtained from the Red Cross Loan Cupboard.

The V.O.N. nurse showed the patient's husband how to change her position in bed, how to support her feet so the bed covers did not pull on them, how to carry out many of the simpler sick-room duties. He was a willing learner, anxious to provide 24-hour care for his wife. He did the washing, prepared the food his wife asked for, helped the nurse at every opportunity. She valued his aid especially because, like many elderly, sick people, her patient was often difficult and unco-operative. All the while, the husband kept his little corner grocery store open for business too.

During this period in bed the V.O.N. nurse bathed the patient regularly, exercised her arms and legs, took measures to prevent deformity and to maintain bodily functions.

Finally the day arrived when the patient was able to sit up in a chair. The nurse showed the husband how to lift his wife into the chair. The next step came when the patient was allowed to bear her weight on her foot. Although the V.O.N. nurse had tried to prevent her from crossing her legs while in bed, she had insisted on doing so and this made her first steps more difficult. A wheelchair now came in handy as the elderly woman needed to sit up longer periods each day to regain her balance and cut down her periods of sleep.

It was the wheelchair that finally made her realize she was really home again and on the mend. She had been mixed up because her bed had been in the living room. But a trip to the kitchen in the wheelchair brought the exclamation, "Oh, I'm really home."

Several months after she had come home, the patient's rehabilitation had reached the point where she could walk short distances with some support from her husband and could be wheeled out of doors onto the verandah. She could eat her meals unassisted at the kitchen table and sit up most of the day.

She had come home helpless and discouraged but with the daily calls of the V.O.N. nurse and the devoted assistance of her husband, she had come a long way back on the road to health.

Doctor Required

Wanted Doctor to locate in modern city of 1,000 in Red River Valley of North Dakota. Fine Clinic Building available. Financial assistance available for equipment, etc., on very reasonable terms. Write: H. M. Nash, Secretary, Community Medical Center, Hatton, North Dakota.

Medical Practitioner Required

Wanted qualified Medical Practitioner for Strathclair Medical Care District covering South part of Municipality. Large area for private practice available. For further particulars, apply to W. H. Morcom, Secretary-Treasurer, R. M. of Strathclair, Strathclair, Manitoba.

Doctor Required

Wanted — Doctor for Rural Municipality of Silver Creek, consisting of six townships, with the Villages of Angusville and Silverton. (Doctor's territory is not limited to this district). The municipal roads are exceptionally good with No. 45 highway 13 miles to Rossburn Hospital, 14 miles to Russell Sacred Heart Hospital.

The municipality provides a five room house with automatic oil furnace, rent free, plus $500.00 a year as health officer. There is also an Indian reservation close by.

Write: Mr. Adam Chaytor, Secretary Treasurer of Rural Municipality of Silver Creek, P.O. Angusville, Man.

Internist Required

WANTED: Internist—thriving North Dakota community. Starting salary $1,000 a month plus expenses. Partnership, 2 years if mutually agreed. Possible to net $25,000 third year. If interested write Box 401, Manitoba Medical Review, 601 Medical Arts Building, Winnipeg 1, Man.